

**THERAPEUTICS
IN INTERNAL MEDICINE**

THERAPEUTICS IN INTERNAL MEDICINE

Edited by

FRANKLIN A. KYSER, M.D., M.S., F.A.C.P.

Associate in Medicine Northwestern University Medical School Chicago
Attending Physician Evanston Hospital Evanston Illinois

THOMAS NELSON & SONS

Edinburgh NEW YORK Toronto

PREFACE

In the past 15 years remarkable progress has been made in the diagnosis and treatment of medical diseases. New knowledge has been gained as a result of intensive laboratory research, clinical investigation,

ment of disease has become so complex that no one individual can claim intimate knowledge of all forms of therapy. In compiling this volume on therapeutics it was felt that the book would attain its maximal value to students and practicing physicians if the subject matter were written by a group of outstanding men whose investigations and teaching experience in certain phases of internal medicine qualify them to make authoritative statements. Such a group of contributors has written this book and when ever possible, individual preferences regarding therapy have been stressed but not to the exclusion of other commonly accepted practices.

The basic plan of the book is to include material related only to the treatment of medical diseases. Since many texts are avail-

able giving detailed information regarding etiology and clinical descriptions no general attempt has been made to include such material in this volume. However, in certain sections, physiologic principles, classifications of disease, and etiologic factors have had to be correlated with treatment in order to cover the subject adequately. Conditions which are

countered by the internist are presented.

The editor gratefully acknowledges the co-operation of the contributors in preparing the material for this book. The stimulating advice of Dr. Frederick Christopher, the technical help of Mrs. Jessie O'Connell, and the suggestions of the publishers have all been of invaluable aid.

The editor sincerely hopes that this book will be of value in the dissemination of knowledge regarding the prevention and treatment of medical diseases.

FRANKLIN A. KYSER, M.D.

636 Church Street
Evanston, Illinois
April, 1950

CONTRIBUTORS

- STEPHEN L. ALDRICH, M D Fairly Research Fellow in Medicine, St Luke's Hospital, Chicago
- M DAVID ALLWEISS, M D Associate in Medicine, Northwestern University Medical School, Adjunct in Internal Medicine, Michael Reese Hospital, Chicago
- WALTER C ALVAREZ, M D Editor in Chief, *The General Practitioner*, Chicago, formerly Consultant in Medicine Mayo Clinic, Rochester Minn
- MILTON W ANDERSON M D, M S in Medicine Instructor in Medicine Mayo Foundation, Graduate School of the University of Minnesota Consultant Section on Cardiology, Mayo Clinic, Rochester, Minn
- J ARNOLD BARGEN, M D M S Professor of Medicine, Mayo Foundation, University of Minnesota, Chief, Department of Intestinal Diseases, Mayo Clinic, Consulting Physician, St Mary's, Kahler, Colonial, and Worrall Hospitals, Rochester, Minn
- ELMER C BARTIS, M D Consultant in Medicine, Lahey Clinic, Attending Physician, New England Baptist and New England Deaconess Hospitals, Boston
- EDWIN D BAYRD M D, M S Instructor in Medicine, Graduate School of the University of Minnesota, St Paul, Minn
- SAMUEL BELLETT, M D, F A C P Assistant Professor of Cardiology, Graduate School of Medicine, University of Pennsylvania, Cardiologist, Philadelphia General Hospital, Staff of Robinette Foundation, University of Pennsylvania, Philadelphia
- JOHN M BERKMAN, M D, M S Associate Professor of Medicine, Mayo Foundation, University of Minnesota, Consultant in Medicine, Mayo Clinic, Rochester, Minn
- BENJAMIN BOSHER, M D Assistant Professor, Department of Nervous and Mental Diseases, Northwestern University Medical School, Attending Physician, Passavant Memorial and St Luke's Hospitals, Chicago, Senior Consultant in Neurology, Veterans Administration Hospital, Hines, Ill
- FREDERICK I BRADY, M D Assistant Chief, Department of Medicine, St. Louis University School of Medicine, St. Louis
- GORONVY O BROWN, M D, A B, F A C P Professor of Internal Medicine, St. Louis University School of Medicine, Consulting Physician, St. Louis City Hospital, Attending Staff, Firmin Desloge Hospital, St. Louis
- J LAMAR CALLAWAY, M D, B S Professor of Dermatology and Syphilology, Duke University School of Medicine, Durham, N C
- RICHARD B CAPPS, M D, F A C P Assistant Professor of Medicine, Northwestern University Medical School, Senior Attending Physician, St. Luke's Hospital, Chicago
- JAMES B CAREY, M D, B S, M B, F A C P Clinical Associate Professor of Medicine, University of Minnesota, Consultant in Gastroenterology and Gastroscopy, University of Minnesota Hospitals, Consultant in Medicine, Nicollet Clinic, Attending Staff, Estel Hospital, Minneapolis
- SANDY B CARTER, M D Assistant in Medicine, Emory University Medical School, Attending Staff, Emory University, Piedmont, St. Joseph's, Crawford Long, and Georgia Baptist Hospitals, Atlanta
- DAVID CAYER, M D, A B, F A C P Assistant Professor of Medicine, the Bowman Gray School of Medicine of Wake Forest College, Winston Salem, N C
- LOWELL T COGGESHALL, M D, A B, A M, LL D (Hon): Professor and Chairman, Department of Medicine, Dean of Division of Biological Sciences, University of Chicago, Chicago
- ARTHUR R COLWELL, M D, S B, Irving S Cutter Professor of Medicine, Chairman, Department of Medicine, Northwest

- University Medical School, Attending Physician, Evanston Hospital Evanston Ill, Consulting Physician, Wesley Memorial Hospital and Municipal Tuberculosis Sanatorium Chicago
- A C CONCORAN, M D Assistant Director of Research, Cleveland Clinic Foundation Cleveland
- DAVID N DANFORTH M D Ph D Assistant Professor of Obstetrics and Gynecology Northwestern University Medical School, Chief, Department of Obstetrics and Gynecology, Evanston Hospital Evanston, Ill
- WILLIAM J DARBY, M D, Ph D Professor of Biochemistry, Assistant Professor of Medicine, Vanderbilt University School of Medicine Assistant Visiting Physician, Vanderbilt University Hospital, Nashville
- FRED L DEY M D, Ph D Natick, Conn
- RALPH E DOLKART M D MS Assistant Professor of Medicine Northwestern University Medical School Associate Attending Physician St Luke's Hospital, Chicago
- MARTIN EPSTEIN M D Chief Resident Department of Medicine University Hospital of Cleveland, Cleveland
- JAMES I FARRELL M D Ph D Assistant Professor of Urology Northwestern University Medical School, Attending Physician and Head Department of Urology, Evanston Hospital Evanston, Ill
- ARTHUR H FLOWER JR, M D Instructor in Dermatology and Syphilology, Duke University School of Medicine Durham NC
- LOUIS L FRIEDMAN, M D MS Former Assistant Professor of Medicine Medical College of Alabama Medical Advisor, National Tuberculosis Association, Consultant Jefferson County Tuberculosis Sanatorium Attending Staff, Jefferson Hillman Norwood Carraway Methodist, and East End Memorial Hospitals, Birmingham, Consultant Diseases of the Chest, Veterans Hospital, Tuscaloosa Ala
- STANLEY GIBSON, M D Professor Emeritus and Former Chairman, Department of Pediatrics, Northwestern University Medical School, Chief of Staff Emeritus, Children's Memorial Hospital, Chicago
- N C GILBERT, M D Professor Emeritus and Former Chairman, Department of Medicine, Northwestern University Medical School, Senior Attending Physician, St Luke's Hospital Chicago
- HERMAN GOLD, M D Chief of Medical Service, Chester Hospital, Chester, Pa
- GEORGE C GRIFFITH, M D, F A C P Clinical Professor of Medicine, University of Southern California School of Medicine, Attending Physician and Chief of Cardiac Clinics, Los Angeles County Hospital, Los Angeles Consultant McCormack General Hospital, Pasadena, Consultant, Birmingham Veterans Administration Hospital, Van Nuys, Calif
- MILTON GROSSMAN, M D Former Chief Resident and Fellow, Cardiovascular Department, Michael Reese Hospital, Chicago
- CLIFFORD C GRULEE, JR, M D Assistant Professor of Pediatrics, Tulane University Medical School New Orleans
- BYRON E HALL, M D, M A, Ph D F A C P Associate Professor of Medicine, Mayo Foundation, University of Minnesota Consultant in Medicine, Mayo Clinic, Rochester, Minn
- ROBERT J HASTERLIK, M D S B Assistant Professor of Medicine, University of Chicago, Senior Physician and Director of Health Service, Argonne National Laboratory, Chicago
- JEROME R HEAD, M D, A M Assistant Professor of Surgery, Northwestern University Medical School, Senior Attending Staff Wesley Memorial Hospital, Chicago, Medical Director, Edward Sanatorium, Naperville, Ill
- ROBERT W HEINLE, M D Associate Professor of Medicine, Western Reserve University, Associate Physician, University Hospitals Cleveland
- LOUIS G HERRMANN, M D, F A C S Associate Professor of Surgery, College of Medicine, University of Cincinnati, Director, Vascular Disease Services, Cincinnati General Hospital and Christian R Holmes Hospital, Associate Surgeon, Children's Hospital, Cincinnati
- FREDERICK HILLER, M D Associate Professor, Department of Nervous and Mental Diseases, Northwestern University Medical School, Attending Physician, Wesley Memorial Hospital, Chicago

- GLADYS L. HOBBY, Ph D : Instructor in Bacteriology, College of Physicians and Surgeons, Columbia University, New York
- ARCHIBALD L. HOYNE, M.D., B.S., F.A.C.P. Emeritus Clinical Professor of Pediatrics (Rush), University of Illinois School of Medicine, Attending Physician, Cook County Hospital, Attending Physician, Children's Memorial Hospital, Consultant St Vincent's Infant Asylum and Maternity Hospital, Chicago
- I. FOREST HUDDLESON, B.S., D.V.M., M.S., Ph.D. Research Professor, Department of Bacteriology and Public Health, Michigan State College, East Lansing, Mich
- HENRY R. JACOBS, M.D. Associate Professor of Medicine, Northwestern University Medical School, Consultant in Tropical Diseases, Veterans Administration, Vaughn General Hospital, Senior Attending Physician, Evanston Hospital, Evanston, Ill
- LOUIS N. KATZ, M.D., M.A., F.A.C.P. Director of Cardiovascular Research, Michael Reese Hospital, Professorial Lecturer in Physiology, University of Chicago, Chicago
- JOSEPH B. KIRSNER, M.D., Ph.D. Associate Professor of Medicine, University of Chicago, Chicago
- FRANKLIN A. KYSER, M.D., M.S., F.A.C.P. Associate in Medicine, Northwestern University Medical School, Attending Physician, Evanston Hospital, Evanston, Ill
- WALTER F. KVALE, M.D., M.S. in Medicine, F.A.C.P. Assistant Professor of Medicine, Mayo Foundation, Graduate School of the University of Minnesota, Consultant in Medicine, Mayo Clinic, Rochester, Minn
- EATON M. MACKAY, M.D. Director of Research, Scripps Metabolic Clinic, La Jolla, Civilian Consultant, San Diego Naval Hospital, San Diego, Calif
- ARTHUR E. MAILLE, M.D., B.S., M.S. in Pathology, F.A.C.P. Assistant Professor of Medicine, Northwestern University Medical School, Senior Attending Physician, Wesley Memorial Hospital, Chicago
- CAREY P. MCCORD, M.D., LL.D. Medical Director, Industrial Health Conservancy Laboratories, Detroit
- KARL F. MEYER, M.D. Professor of Experimental Pathology and Director, Hooper Foundation, University of California Medical Center, San Francisco
- WINSTON R. MILLER, M.D., M.A. Consultant in Medicine, Interstate Clinic, Attending Physician, St John's and Red Wing City Hospitals, Red Wing, Minn
- WILLIAM E. MOLLE, M.D., B.S. Instructor in Medicine, College of Medical Evangelists, Attending Physician, Los Angeles County Hospital, Consulting Gastroenterologist, St John's Hospital, Santa Monica, Calif
- LESTER M. MORRISON, M.D. Assistant Professor of Medicine, College of Medical Evangelists, Senior Attending Physician, Los Angeles County Hospital, Los Angeles
- FRANCIS D. MURPHY, M.D., B.S., M.S. Professor and Head, Department of Medicine, Marquette University School of Medicine, Medical Director, Milwaukee County Hospital, Chief of Staff, St Joseph's Hospital, Milwaukee
- DONALD R. NICHOLS, M.D., M.S., F.A.C.P. Consultant in Medicine, Mayo Clinic, Assistant Professor of Medicine, Mayo Foundation, Graduate School of the University of Minnesota, Rochester, Minn
- EDWARD A. OLIVER, M.D., A.B. Professor Emeritus and Former Chairman, Department of Dermatology, Northwestern University Medical School, Chicago
- IRVINE H. PAGE, M.D. Director of Research, Cleveland Clinic Foundation, Cleveland
- WALTER L. PALMER, M.D., Ph.D., F.A.C.P. Professor of Medicine, University of Chicago School of Medicine, Chicago
- ROBERT T. PARKER, M.D., M.S. in Medicine Assistant Professor of Medicine, Mayo Foundation, Graduate School of the University of Minnesota, Consultant, Section in Cardiology, Mayo Clinic, Rochester, Minn
- EDWARD L. PRATT, M.D. National Research Council Senior Fellow in Pediatrics, Instructor in Pediatrics, Harvard Medical School, Associate Physician, Infants and Children's Hospital, Boston
- HOBART A. REIMANN, M.D. Professor of Medicine, Jefferson Medical College and Hospital, Philadelphia
- RICHARD K. RICHARDS, M.D., F.A.C.P., F.I.C.A. Associate Director of Pharmacologic Research, Abbott Laboratories, North Chicago, Professorial Lecturer in Pharmacology, Northwestern University Medical School, Chicago

- PAUL S RHODES, M D, F A C P** Professor of Medicine, Northwestern University Medical School, Chairman, Department of Medicine, Wesley Memorial Hospital, Attending Staff, Cook County Contagious Hospital, Chicago
- EDWARD F ROSENBERG, M D, M S** in Internal Medicine Ph D in Internal Medicine Assistant Professor of Medicine, Chicago Medical School, Attending Staff, Department of Medicine, Chief, Arthritis Clinic, Michael Reese Hospital, Chicago
- LUDWIG T ROSENTHAL, M D** Instructor in Medicine, College of Medical Evangelists, Attending Physician, Los Angeles County Hospital, Los Angeles
- RENO ROSI, M D** Associate in Medicine, Northwestern University Medical School, Attending Physician, Wesley Memorial Hospital and Cook County Contagious Disease Hospital, Chicago
- LOUIS WENDLIN SAUER, M D, Ph D** Assistant Professor of Pediatrics, Northwestern University Medical School, Attending Physician, Evanston Hospital, Evanston, Ill
- RICHARD MONTGOMERY SHICK, M D, M S, F A C P** Consultant in Medicine, Mayo Clinic, Instructor in Medicine, Mayo Foundation Graduate School of the University of Minnesota, Rochester, Minn
- MARTIN SEIFERT, M D** Associate in Medicine, Northwestern University Medical School, Attending Physician and Chief of Contagious Disease Service, Evanston Hospital, Evanston, Ill
- LEROY H SLOAN, M D, F A C P** Professor of Medicine, University of Illinois School of Medicine, Attending Physician, Illinois Central Hospital, Chicago, Ill
- LOWELL D SNORE, M D, F A C P** Associate Professor of Medicine, Northwestern University Medical School, Chief, Department of Medicine, Evanston Hospital, Evanston, Ill
- JOHN C SNYDER, M D** Professor of Public Health Bacteriology, Harvard University School of Public Health, Boston
- JACOB HYAMS SWARTZ, M D** Assistant Professor of Dermatology, Harvard Medical School and Postgraduate School, Dermatologist, Massachusetts General Hospital, Boston
- VERNON C TURNER, M D, F A C S** Associate in Bone and Joint Surgery, Northwestern University Medical School, Chief, Department of Orthopedic Surgery, Evanston Hospital, Evanston Ill
- TERENCE LLOYD TYSON, M D, F A C P** Attending Physician, Presbyterian Hospital, Physician, Arthritis Clinic, Vanderbilt Clinic of Presbyterian Hospital, Arthritis Clinic, New York Orthopedic Hospital, Associate Consulting Internist, Institute of Ophthalmology of the Presbyterian Hospital, New York
- LEON UNGER, M D, F A C P** Associate Professor of Medicine, Northwestern University Medical School, Attending Physician Cook County Hospital and Wesley Memorial Hospital, Chicago
- ANDREW YEOMANS, M D** Assistant Professor of Medicine, Dartmouth Medical School, Hanover, N H, Chief, Medical Service, Veterans Administration Hospital, White River Junction, Vt

CONTENTS

CHAPTER I THE INFECTIOUS DISEASES

DISEASES DUE TO VIRUSES

THE COMMON COLD	1
RENO ROSI	
INFLUENZA	4
RENO ROSI	
PSITTACOSIS	6
KARL F MEYER	
HERPES ZOSTER	10
RENO ROSI	
MEASLES	11
RENO ROSI	
RUBELLA	14
RENO ROSI	
MUMPS	14
RENO ROSI	
CHICKENPOX	16
RENO ROSI	
SMALLPOX	16
LOUIS W SAUER	
SMALLPOX VACCINATION (VACCINIA)	17
LOUIS W SAUER	
RABIES	19
MARTIN SEIFERT	
ACUTE POLIOMYELITIS	25
CLIFFORD G GRULEE JR	
DENGUE FEVER	34
HENRY B JACOBS	
YELLOW FEVER	34
HENRY B JACOBS	
PHLEBOTOMUS FEVER	35
HENRY R JACOBS	
FOOT AND MOUTH DISEASE	36
HENRY B JACOBS	
LYMPHOGRANULOMA VENEREUM	36
JAMES I FARRELL	
ACUTE GASTRO ENTERITIS	36
RICHARD B CAPPS	
ACUTE INFECTIOUS HEPATITIS AND HOMOLOGOUS SERUM HEPATITIS	37
RICHARD B CAPPS	

DISEASES DUE TO BACTERIA

THE PNEUMONIAS	39
PAUL S RHODES	
MENINGOCOCCAL MENINGITIS	47
ARCHIBALD L HOYNE	
INFLUENZAL MENINGITIS	51
ARCHIBALD L HOYNE	
PNEUMOCOCCAL MENINGITIS	54
ARCHIBALD L HOYNE	
STREPTOCOCCAL AND STAPHYLOCOCCAL MENINGITIS	57
ARCHIBALD L HOYNE	
TUBERCULOUS MENINGITIS	60
ARCHIBALD L HOYNE	
SCARLET FEVER	63
GEORGE C GRIFFITH	
RHEUMATIC FEVER AND CHOREA	65
GEORGE C GRIFFITH	
ERYSIPELAS	72
GEORGE C GRIFFITH	
GONORRHEA	72
JAMES I FARRELL	
CHANCROID INFECTION	75
JAMES I FARRELL	
BRUCELLOSIS	75
I FOREST HUDDLESON	
TULAREMIA	77
LEE FOSHAY	
DIPHTHERIA	80
LOUIS W SAUER	
PERTUSSIS	84
LOUIS W SAUER	
TYPHOID FEVER	88
DONALD R NICHOLS	
SALMONELLOSIS	92
DONALD R NICHOLS	
BACILLARY DYSENTERY	94
DONALD R NICHOLS	
CHOLERA	96
HOBART A REIMANN	
PLAGUE	99
HOBART A REIMANN	
LEPROSY	100
HOBART A REIMANN	
TETANUS	101
EDWARD L PRATT	
ANTHRAX	104
HEJMAN GOLD	

GLANDERS	107	RAT BITE FEVER	157
WINSTON R MILLER		HENRY H JACOBS	
MELIOIDOSIS	108	TOXOPLASMOSIS	157
WINSTON R MILLER		FRANKLIN A KYSER	
TUBERCULOSIS	109	LEISHMANIASIS	158
JEROME H HEAD		HENRY H JACOBS	
GENTO URINARY TUBERCULOSIS	128	AFRICAN TRYPANOSOMIASIS	161
JAMES I FARRELL		HENRY H JACOBS	
		SOUTH AMERICAN TRYPANOSOMIASIS	161
		HENRY R JACOBS	
FUNGUS DISEASES		GRANULOMA INGUINALE	162
ACTINOMYCOSIS	131	HENRY R JACOBS	
JACOB H SWARTZ		SYPHILIS	163
BLASTOMYCOSIS	132	J LAMAR CALLAWAY AND	
JACOB H SWARTZ		ARTHUR H FLOWER, JR	
COCCIDIOIDOMYCOSIS	134	TROPICAL TREPONEMATOSIS	166
JACOB H SWARTZ		J LAMAR CALLAWAY AND	
HISTOPLASMOSIS	135	ARTHUR H FLOWER, JR	
JACOB H SWARTZ		PINTA	167
MONILIASIS	136	J LAMAR CALLAWAY AND	
JACOB H SWARTZ		ARTHUR H FLOWER, JR	
ASPERGILLOSIS	140	BEJEL	188
JACOB H SWARTZ		J LAMAR CALLAWAY AND	
CRYPTOCOCCOSIS	141	ARTHUR H FLOWER, JR	
JACOB H SWARTZ		AMEBIASIS	189
SPOROTRICHOSIS	142	RALPH E DOLKART AND	
JACOB H SWARTZ		FRED L DEY	
MADUROMYCOSIS	142	FLAGELLATE DYSENTERY	194
JACOB H SWARTZ		RALPH E DOLKART AND	
GEOTRICHOSIS	143	FRED L DEY	
JACOB H SWARTZ			
		DISEASES OF DOUBTFUL ORIGIN	
RICKETTSIAL DISEASES		ERYTHEMA NODOSUM	195
THE RICKETTSIOSES	143	RALPH E DOLKART AND	
JOHN C SNYDER AND		FRED L DEY	
ANDREW YEOMANS		DISSEMINATED LUPUS ERYTHEMATOSUS	196
		RALPH E DOLKART AND	
		FRED L DEY	
BARTONELLA DISEASE		INFECTIOUS PLEURODYNIA	197
OROYA FEVER AND VERRUGA PERUANA	147	RALPH E DOLKART AND	
FRANKLIN A KYSER		FRED L DEY	
		REITER'S DISEASE	197
		RALPH E DOLKART AND	
		FRED L DEY	
PROTOZOAN DISEASES		RELAPSING FEBRILE NODULAR NON-	
LEPTOSPIROSIS	147	SUPPURATIVE PANNICULITIS	197
HENRY R JACOBS		RALPH E DOLKART AND	
MALARIA	148	FRED L DEY	
LOWELL T COGGESHALL			
BLACKWATER FEVER	154	ADDENDUM TERRAMYCIN	198
LOWELL T COGGESHALL		TERENCE L TYSON AND	
RELAPSING FEVER	155	GLADYS L HOBBY	
HENRY R JACOBS			

CHAPTER II PARASITIC DISEASES

FLUKE INFECTIONS OTHER THAN		TRICHINOSIS	212
SCHISTOSOMIASIS	205	FREDERICK J BRADY	
FREDERICK J BRADY		ANCYLOSTOMIASIS	212
SCHISTOSOMIASIS	205	FREDERICK J BRADY	
FREDERICK J BRADY		FILARIASIS	214
SWIMMER'S ITCH	207	FREDERICK J BRADY	
FREDERICK J BRADY		FILARIASIS OTHER THAN BANCROFT'S	
TAPEWORM INFECTIONS	207	FILARIASIS	216
FREDERICK J BRADY		FREDERICK J BRADY	
ASCARIASIS	209	GUINEA WORM INFECTION	217
FREDERICK J BRADY		FREDERICK J BRADY	
ENTEROBIASIS	210		
FREDERICK J BRADY			

CHAPTER III DISEASES OF METABOLISM

DIABETES MELLITUS	218	OBESITY	246
ARTHUR R COLWELL		EATON M MACKAY	
HEMOCHROMATOSIS	243	DIABETES INSIPIDUS	251
ARTHUR R COLWELL		EATON M MACKAY	
HYPERINSULINISM	243	ACIDOSIS AND ALKALOSIS	253
EATON M MACKAY		EATON M MACKAY	

CHAPTER IV DISEASES OF THE GLANDS OF
INTERNAL SECRETIONDISEASES OF THE SUPRARENAL
GLANDS

ADDISON'S DISEASE	256
M DAVID ALLWEISS	

THYROID DISEASE

HYPERTHYROIDISM	260
ELMER C BARTELS	
HYPOTHYROIDISM	268
ELMER C BARTELS	
THYROIDITIS	271
ELMER C BARTELS	
THE PARATHYROID GLANDS	272
GEORGE O BELL	

OVARIAN DISEASE

AMENORRHEA AND HYPOMENORRHEA	276
DAVID N DANFORTH	
MENORRHAGIA AND METRORRHAGIA	278
DAVID N DANFORTH	
DYSMENORRHEA	279
DAVID N DANFORTH	
THE MENOPAUSE	281
DAVID N DANFORTH	

TESTICULAR DISEASE

STERILITY IN THE MALE	283
JAMES I FARRELL	
IMPOTENCE	285
JAMES I FARRELL	

CHAPTER V DEFICIENCY DISEASES

VITAMIN DEFICIENCIES		VITAMIN C DEFICIENCY		297
GENERAL CONSIDERATIONS	288	DAVID CAYER		
DAVID CAYER		VITAMIN D DEFICIENCY	299	
VITAMIN A DEFICIENCY	290	DAVID CAYER		
DAVID CAYER		VITAMIN K DEFICIENCY	303	
VITAMIN B THIAMINE DEFICIENCY	292	DAVID CAYER		
DAVID CAYER		THE SPRUE SYNDROME	307	
VITAMIN B NIACIN DEFICIENCY	294	WILLIAM J DARBY		
DAVID CAYER		ANOREXIA NERVOSA	309	
VITAMIN B RIBOFLAVIN DEFICIENCY	296	JOHN M BERKMAN		
DAVID CAYER		NUTRITIONAL EDEMA	313	
		WILLIAM J DARBY		

CHAPTER VI DISEASES OF THE DIGESTIVE TRACT

DISEASES OF THE MOUTH ESOPHAGUS, AND STOMACH		FUNCTIONAL DISORDERS OF THE COLON		344
VINCENT'S ANGINA	314	WALTER L PALMER AND		
ARTHUR E MAHLE		JOSEPH B MIRSNER		
STOMATITIS	315	DIVERTICULOSIS AND DIVERTICULITIS	348	
ARTHUR E MAHLE		WALTER L PALMER AND		
ESOPHAGITIS	316	JOSEPH B MIRSNER		
ARTHUR E MAHLE		DISEASES OF THE LIVER AND BILIARY TRACT		
PEPTIC ULCER OF THE ESOPHAGUS	317	TOXIC HEPATITIS	349	
ARTHUR E MAHLE		WILLIAM E MOLLE AND		
CARDIOSPASM	318	LESTER M MORRISON		
ARTHUR E MAHLE		ACUTE YELLOW ATROPHY OF THE LIVER	351	
PYLOROSPASM	320	LESTER M MORRISON		
ARTHUR E MAHLE		PORTAL CIRRHOSIS OF THE LIVER	352	
HYPERCHLORHYDRIA AND HYPOCHLORHYDRIA	320	LESTER M MORRISON		
ARTHUR E MAHLE		HEPATIC INSUFFICIENCY	355	
GASTRITIS	321	LUDWIG T ROSENTHAL AND		
JAMES B CAREY		LESTER M MORRISON		
PEPTIC ULCER GASTRIC AND DUODENAL	324	PREOPERATIVE PREPARATION OF THE JAUNDICED PATIENT	357	
JAMES B CAREY		CONORVY O BROWN		
DISEASES OF THE SMALL BOWEL AND COLON		ACUTE CHOLECYSTITIS	360	
REGIONAL ENTERITIS	332	CONORVY O BROWN		
J ARNOLD BARGEN		CHRONIC NONCALCULOUS CHOLECYSTITIS	361	
ALIMENTARY TUBERCULOSIS	334	CONORVY O BROWN		
J ARNOLD BARGEN		DISEASES OF THE PANCREAS		
CHRONIC THROMBO ULKERATIVE (STREPTOCOCCAL) COLITIS	336	ACUTE PANCREATITIS	362	
J ARNOLD BARGEN		LOWELL D SNORF		
REGIONAL (SEGMENTAL) ULKERATIVE COLITIS	343	CHRONIC PANCREATITIS	364	
J ARNOLD BARGEN		LOWELL D SNORF		
		CELIAC SYNDROME	366	
		LOWELL D SNORF		

CHAPTER VII DISEASES OF THE RESPIRATORY TRACT

DISEASES OF THE TRACHEA
AND BRONCHI

ACUTE AND CHRONIC LARYNGITIS	368
LOUIS L. FRIEDMAN AND SANDY B. CARTER	
ACUTE TRACHEOBRONCHITIS	369
LOUIS L. FRIEDMAN AND SANDY B. CARTER	
CHRONIC BRONCHITIS AND BRONCHI ECTASIS	370
LOUIS L. FRIEDMAN AND SANDY B. CARTER	
EMPHYSEMA	374
LOUIS L. FRIEDMAN AND SANDY B. CARTER	
PULMONARY FIBROSIS	376
LOUIS L. FRIEDMAN AND SANDY B. CARTER	
COLLAPSE OF THE LUNG ATELECTASIS	376
LOUIS L. FRIEDMAN AND SANDY B. CARTER	
PULMONARY EMBOLISM	378
LOUIS L. FRIEDMAN AND SANDY B. CARTER	
PNEUMONOCOCCIOSIS	381
LOUIS L. FRIEDMAN AND SANDY B. CARTER	
PULMONARY ABSCESS	382
LOUIS L. FRIEDMAN AND SANDY B. CARTER	

DISEASES OF THE PLEURA AND
PLEURAL CAVITY

ACUTE PLEURISY	384
LOUIS L. FRIEDMAN AND SANDY B. CARTER	
PLEURISY WITH EFFUSION	385
LOUIS L. FRIEDMAN AND SANDY B. CARTER	
LOFFLER'S SYNDROME	386
LOUIS L. FRIEDMAN AND SANDY B. CARTER	
EMPHYEMA	387
LOUIS L. FRIEDMAN AND SANDY B. CARTER	
PNEUMOTHORAX	388
LOUIS L. FRIEDMAN AND SANDY B. CARTER	

DISEASES OF THE MEDIASTINUM

INFLAMMATION OF THE MEDIASTINUM	389
LOUIS L. FRIEDMAN AND SANDY B. CARTER	
SPONTANEOUS MEDIASTINAL EMPHYSEMA	390
LOUIS L. FRIEDMAN AND SANDY B. CARTER	

FUNCTIONAL RESPIRATORY DISEASE

HYPERVENTILATION SYNDROME	390
LOUIS L. FRIEDMAN AND SANDY B. CARTER	
HICCUGH	392
LOUIS L. FRIEDMAN AND SANDY B. CARTER	

CHAPTER VIII DISEASES OF THE CARDIOVASCULAR
SYSTEM

DISEASES OF THE HEART

THERAPEUTIC IMPLICATIONS OF CARDIAC CATHETERIZATION	394
GEORGE C. CRIFTH	
CONGENITAL HEART DISEASE	395
STANLEY GIBSON	
THE CARDIAC ARRHYTHMIAS	399
NEWELL C. GILBERT	
NEUROCIRCULATORY ASTHENIA OR THE EFFORT SYNDROME	405
NEWELL C. GILBERT	

CORONARY INSUFFICIENCY WITH ANGINA
PECTORIS

MILTON W. ANDERSON AND ROBERT L. PARKER	408
ACUTE MYOCARDIAL INFARCTION	414
ROBERT L. PARKER AND MILTON W. ANDERSON	
SUBACUTE BACTERIAL ENDOCARDITIS	424
MILTON GROSSMAN AND LOUIS N. KATZ	

ACUTE BACTERIAL ENDOCARDITIS MILTON GROSSMAN AND LOUIS N KATZ	429	PERIARTERITIS NODOSA RICHARD M SHICK AND WALTER F KVALE	458
ACUTE MYOCARDITIS OF INFECTIOUS DISEASE FRANKLIN A KYSER	431	TEMPORAL ARTERITIS RICHARD M SHICK AND WALTER F KVALE	458
CHRONIC VALVULAR DISEASE FRANKLIN A KYSER	431	ARTERIOSCLEROSIS OBLITERANS AND THROMBOANGITIS OBLITERANS	459
PERICARDITIS FRANKLIN A KYSER	432	RICHARD M SHICK AND WALTER F KVALE	
HEART DISEASE IN PREGNANCY FRANKLIN A KYSER	434	SUDDEN ARTERIAL OCCLUSION RICHARD M SHICK AND WALTER F KVALE	466
HEART DISEASE IN THE SURGICAL PATIENT FRANKLIN A KYSER	435	RAYNAUD'S DISEASE	468
CARDIAC TRAUMA FRANKLIN A KYSER	437	RICHARD M SHICK AND WALTER F KVALE	
CARDIAC DECOMPENSATION SAMUEL BELLET	437	LIVEDO RETICULARIS AND ACROCYANOSIS RICHARD M SHICK AND WALTER F KVALE	469
DISEASES OF THE BLOOD VESSELS		ERYTHROMELALGIA RICHARD M SHICK AND WALTER F KVALE	470
HYPERTENSIVE VASCULAR DISEASE IRVINE H PAGE AND A C CORCORAN	448	SCLERODERMA RICHARD M SHICK AND WALTER F KVALE	471
DISSECTING ANEURYSM OF THE AORTA LEROY H SLOAN	455	PHLEBOTROMBOSIS AND THROMBO PHLEBITIS LOUIS C HERRMANN	472
ORTHOSTATIC (POSTURAL) HYPOTENSION RICHARD M SHICK AND WALTER F KVALE	457		

CHAPTER IX DISEASES OF THE BLOOD AND BLOOD FORMING ORGANS

MACROCYTIC HYPERCHROMIC ANEMIAS ROBERT W HEINLE AND MARTIN EPSTEIN	478	AGRANULOCYTOSIS ROBERT W HEINLE AND MARTIN EPSTEIN	489
APLASTIC AND PRIMARY REFRACTORY ANEMIA ROBERT W HEINLE AND MARTIN EPSTEIN	481	INFECTIOUS MONONUCLEOSIS EDWIN D BAYRD	491
HYPPOCHROMIC ANEMIA ROBERT W HEINLE AND MARTIN EPSTEIN	482	THE LEUKEMIAS BYRON E HALL	491
HEMOLYTIC ANEMIA ROBERT W HEINLE AND MARTIN EPSTEIN	484	HODGKIN'S DISEASE AND ALLIED DISORDERS BYRON E HALL	498
ERYTHROBLASTOSIS FETALIS ROBERT W HEINLE AND MARTIN EPSTEIN	485	POLYCYTHEMIA VERA BYRON E HALL	502
SPLenic ANEMIA ROBERT W HEINLE AND MARTIN EPSTEIN	488	HEMOPHILIA EDWIN D BAYRD	506
		PURPURA EDWIN D BAYRD	507
		MULTIPLE MYELOMA EDWIN D BAYRD	510

CHAPTER X DISEASES OF THE URINARY TRACT

ACUTE GLOMERULONEPHRITIS	512	LIPOID NEPHROSIS	524
FRANCIS D MURPHY		FRANCIS D MURPHY	
SUBACUTE GLOMERULONEPHRITIS	515	LOWER NEPHRON NEPHROSIS	525
FRANCIS D MURPHY		FRANCIS D MURPHY	
THE NEPHROTIC SYNDROME	515	PYELITIS AND PYELONEPHRITIS	527
FRANCIS D MURPHY		FRANCIS D MURPHY	
CHRONIC GLOMERULONEPHRITIS	518	CYSTITIS	529
FRANCIS D MURPHY		FRANCIS D MURPHY	
UREMIA	522	RENAL CALCULI	531
FRANCIS D MURPHY		FRANCIS D MURPHY	

CHAPTER XI DISEASES OF THE LOCOMOTOR SYSTEM

RHEUMATOID ARTHRITIS	533	GOUT	550
EDWARD F ROSENBERG		EDWARD F ROSENBERG	
OSTEO-ARTHRITIS	543	FIBROSITIS	556
EDWARD F ROSENBERG		EDWARD F ROSENBERG	
PALINDROMIC RHEUMATISM	545	OSTEITIS DEFORMANS	557
EDWARD F ROSENBERG		VERNON C TURNER	
ARTICULAR DISEASES ASSOCIATED WITH		OSTEOPOROSIS	559
SPECIFIC INFECTIONS	546	VERNON C TURNER	
EDWARD F ROSENBERG		OSTEOMALACIA	560
INTERMITTENT HYDRARTHROSIS	549	VERNON C TURNER	
EDWARD F ROSENBERG		MYASTHENIA GRAVIS	561
		FREDERICK MILLER	

CHAPTER XII DISEASES DUE TO ALLERGY

ALLERGY OF THE NOSE AND NASAL		URTICARIA AND ANGIO-NEUROTIC EDEMA	582
SINUSES	567	LEON UNGER	
LEON UNGER			
BRONCHIAL ASTHMA	574	SERUM SICKNESS	584
LEON UNGER		LEON UNGER	

CHAPTER XIII THE ROLE OF ADRENOCORTICOTROPIC HORMONE (ACTH) AND 17 HYDROXY 11 DEHYDROCORTICOSTERONE (CORTISONE) IN PRESENT DAY THERAPY	589
--	-----

RALPH E DOLKART AND STEPHEN L ALDRICH

CHAPTER XIV DISEASES DUE TO PHYSICAL AGENTS

THERMAL STATES	592	MOUNTAIN SICKNESS	594
CAREY P MCCORD		CAREY P MCCORD	
MOTION SICKNESS	593	DECOMPRESSION DISEASE	594
CAREY P MCCORD		CAREY P MCCORD	

xviii	CONTENTS	
ELECTRIC SHOCK	595	ATOMIC RADIATION INJURIES
CAREY P. MCCORD		ROBERT J. HASTERLIK
CARBON MONOXIDE ASPHYXIA	596	
CAREY P. MCCORD		

CHAPTER XV DISEASES DUE TO INTOXICATIONS

ACUTE ALCOHOLISM	600	MERCURY POISONING	612
RICHARD K. RICHARDS		RICHARD K. RICHARDS	
POISONING WITH METHYL ALCOHOL	602	LEAD POISONING	614
(METHANOL)		RICHARD K. RICHARDS	
RICHARD K. RICHARDS			
BARBITURATE POISONING	603	MANAGEMENT OF BITES BY DOMESTIC	
RICHARD K. RICHARDS		SNAKES	616
BROVIDE INTOXICATION	608	RICHARD K. RICHARDS	
RICHARD K. RICHARDS			
ARSENIC POISONING	610	BLACK WIDOW SPIDER BITE	617
RICHARD K. RICHARDS		RICHARD K. RICHARDS	

CHAPTER XVI DISEASES OF THE NERVOUS SYSTEM

A THERAPEUTIC APPROACH TO PSYCHO		PARKINSONISM	651
SOMATIC PROBLEMS	619	FREDERICK HILLER	
WALTER C. ALVAREZ		EPILEPSY AND THE CONVULSIVE STATE	653
CEREBRAL EMBOLISM THROMBOSIS, AND		BENJAMIN BOSHES	
HEMORRHAGE, INCLUDING CEREBRAL		NARCOLEPSY	659
ARTERIOSCLEROSIS	626	BENJAMIN BOSHES	
FREDERICK HILLER		THE PARAPLEGIC STATE IN LESIONS OF	
SUBARACHNOID HEMORRHAGE	634	THE SPINAL CORD	660
FREDERICK HILLER		FREDERICK HILLER	
HEADACHE	637	NEURITIS AND BELL'S Palsy	666
FREDERICK HILLER		FREDERICK HILLER	
MULTIPLE OR DISSEMINATED SCLEROSIS	647	MÉNIÈRE'S SYNDROME	669
FREDERICK HILLER		FREDERICK HILLER	

CHAPTER XVII DISEASES OF THE SKIN

IMPETIGO CONTAGIOSA	672	PSORIASIS	679
EDWARD A. OLIVER		EDWARD A. OLIVER	
ACNE	672	PITYRIASIS ROSEA	680
EDWARD A. OLIVER		EDWARD A. OLIVER	
MYCOSES OF THE HAIRLESS SKIN	674	LICHEN PLANUS	680
EDWARD A. OLIVER		EDWARD A. OLIVER	
SCABIES	676	ECZEMATOID DERMATITIS	681
EDWARD A. OLIVER		EDWARD A. OLIVER	
ERYTHEMA MULTIFORME	677	TINEA VERSICOLOR	683
EDWARD A. OLIVER		EDWARD A. OLIVER	
DERMATITIS HERPETIFORMIS	677	PRURITUS ANI	684
EDWARD A. OLIVER		EDWARD A. OLIVER	
SEBORRHOIC DERMATITIS	678		
EDWARD A. OLIVER			

**THERAPEUTICS
IN INTERNAL MEDICINE**

THE INFECTIOUS DISEASES

DISEASES DUE TO VIRUSES

COMMON COLD

A specific etiologic agent either bacterial or viral, has not been identified with the disease entity known as the common cold. The highly contagious infections involving the upper respiratory tract are usually classified as "colds." This is in contrast to the infections of the lower respiratory system (influenza, "grippe," etc.), in which more severe systemic symptoms occur. There are no specific therapeutic agents in the treatment of the common cold. Efforts, therefore, should be directed to the early relief of the symptoms of rhinitis, hoarseness, headache, and aching and to the prevention of serious complications. It is also of utmost importance to prevent spread of the disease to other individuals.

General Management. Bed rest for 24 to 48 hours is the most essential factor in treatment. This should not be rigid but vary with the individual case. Bathroom privileges are permitted. Diet and fluid intake require consideration but rarely offer a problem. The diet should be suited to the individual's desire and should be preferably soft. Soft cooked eggs, cereal, milk, egg-nog, and fruit

water, milk, tea, and soups should total 3000 cc. This is easily accomplished by the taking of a glass of liquid every hour. Purgatives, such as castor oil or magnesium sulfate and enemas, are to be avoided but if constipation becomes distressing a mild laxative (milk of magnesia, 15 to 30 cc., or mineral oil 30 cc.) will suffice. Some patients are benefited by profuse sweating which may be accomplished by the ingestion of hot drinks, with or without whiskey, or Dover's

powder, 5 grains (0.36 mg.) every 4 hours for three or four doses. High temperatures if present, are best controlled by the use of aspirin, 10 or 15 grains (0.6 or 1.0 gm.). The generalized aching and headache are also relieved by a similar dose of aspirin but occasionally it is necessary to prescribe codeine phosphate $\frac{1}{4}$ or $\frac{1}{2}$ grain (15 or 30 mg.) for relief. Sore throat may be alleviated by the use of a warm saline or soda gargle ($\frac{1}{2}$ teaspoonful of sodium chloride or sodium bicarbonate to a glass of warm water). The use of throat swabs with 10 per cent argyrol, tr. of iodine or tr. of merthiolate, is to be avoided. Chest pain and discomfort may require the use of a mustard poultice applied to the site of distress for 15 or 20 minutes during which time the skin will flush. Poultices are not frequently prescribed for as much relief may be obtained by the use of aspirin, grains 10 (0.6 gm.) or codeine grain $\frac{1}{2}$ (30 mg.).

Relief from Cough. The most annoying symptom of the common cold is cough. It appears best to suppress rather than obliterate the cough and the drug of choice to meet this end is codeine in dosage great enough to offer relief. Usually $\frac{1}{4}$ or $\frac{1}{2}$ grain (15 or 30 mg.) every 4 to 6 hours is sufficient. The use of expectorants alone or in combination with codeine has been practiced for years. Their effect is usually uncertain. The most widely used and probably the most effective of the expectorants is ammonium chloride, 0.3 gm. to the dose, given every 3 hours. Other expectorants frequently used are as follows: potassium iodide 0.3 gm., sodium iodide 0.3

irritative, excessive, or associated with dysp-

nea the use of an opiate is indicated. The most widely used opiates are codeine, $\frac{1}{4}$ to $\frac{1}{2}$ grain (25 to 300 mg), dilaudid $\frac{1}{4}$ grain (10 mg), pantapone $\frac{1}{2}$ grain (50 mg), and morphine $\frac{1}{4}$ or $\frac{1}{2}$ grain (80 or 100 mg). Except for codeine, the opiates are rarely indicated and in children are contraindicated. Distressing intractable cough is only occasionally seen during the common cold but should it occur and fail to respond to codeine, hycodan bitartrate (Endo) $\frac{1}{2}$ grain (50 mg) may be useful. The following cough prescriptions have been used for years and are usually efficient.

LOOSE COUGH WITH EXPECTORATION

Ammonium chloride 5 to 8 grains (0.3 to 0.5 gm) to dose

		gm or cc
Ammonium chloride	dr iv	160
Syr of citric acid	fl oz	300
Water to make	fl oz	1200

Sig 1 teaspoonful every 3 hours

DRY, IRRITATIVE COUGH WITHOUT EXPECTORATION

		gm or cc
Potassium citrate	dr iv	160
Camphorated tr opium	fl oz i	300
Syr of wild cherry	fl oz ii	600
Water to make	fl oz iv	1200

Sig 1 teaspoonful every 3 hours

USEFUL CODEINE MIXTURES

		gm or cc
(1) Codeine phosphate	gr viiss	0.5
Ammonium chloride	dr iv	160
Syr of citric acid	fl oz i	300
Water to make	fl oz iv	1200

Sig 1 teaspoonful every 3 to 4 hours

		gm or cc
(2) Codeine phosphate	gr iv	0.25
Elixir terpin hydrate to make	fl oz iv	120
Mix		

Sig 1 teaspoonful every 3 hours

		gm or cc
(3) Codeine phosphate	gr iv	0.25
Syr sedulon (Hoffmann LaRoche) to make	fl oz iv	1200
Mix		

Sig 1 teaspoonful every 3 hours

OPiate COUGH MIXTURES

		gm or cc
(1) Dilaudid	gr ss	0.03
Syr of cocoa	fl oz iv	1200

Sig 1 teaspoonful every 3 hours

		gm or cc
(2) Pantapone	gr iss	0.09
Syr of cocoa	fl oz iii	900

Sig 1 teaspoonful every 3 hours

COUGH MIXTURE FOR CHILDREN

		gm or cc
(1) Syr of ipecac	fl dr i	40
Syr of orange	fl oz ii	600

Sig 1 teaspoonful every 3 hours

		gm or cc
(2) Syr of hydnodic acid		
Syr of wild cherry	aa fl oz i	300

Sig 1 teaspoonful every 3 hours

		gm or cc
(3) Calcidrine syrup (Abbott)	fl oz ii	600

Sig 1 teaspoonful every 3 or 4 hours

It is well to remember that the use of steam, plain or medicated, will control a distressing cough when cough mixtures fail. Many types of vaporizers are available. To produce a moist, aromatic, medicated steam one may use tincture of benzoin (1 teaspoonful to 1 quart of boiling water), menthol (10 drops of a 10 per cent alcoholic solution to 1 pint of hot water), or oil of eucalyptus ($\frac{1}{2}$ teaspoonful to 1 pint of boiling water).

Relief from Nasal Obstruction. Therapeutic agents used locally offer the patient temporary relief and the most efficient are the vasoconstrictor drugs. Nose drops of ephedrine sulfate, 0.5 to 10 per cent solution, neo synephrine (Sterns), 0.25 per cent solution, privity hydrochloride (Ciba), 0.25 per cent solution, and tuamine sulfate (Lilly), 2 per cent solution, are of considerable value in eliminating the nasal congestion. Only suspensions placed in the nose are contraindicated, particularly in the very young and the aged because of the danger of lipid pneumonia. The benzedrine sulfate (SKF) inhaler and tuamine sulfate (Lilly) inhaler are helpful and obviate the instillation of a liquid into the nose. It is well not to give benzedrine sulfate or neo synephrine to the hypertensive individual or one with cardiac disease. Atropine sulfate, $\frac{1}{320}$ to $\frac{1}{500}$ gram, will quickly control the rhinorrhea but its unpleasant side effects makes its use undesirable. Nasal tampons of 10 or 20 per cent argyrol (Barnes) and/or 0.5 or 1 per cent ephedrine sulfate are valuable.

able in the later stages of the disease when the nasal secretions become thick tenacious and difficult to dislodge

Use of Sulfonamides and Antibiotics
The routine use of the sulfonamides penicillin aureomycin and other antibiotics is rarely indicated and should be reserved for the individual showing signs of secondary bacterial invasion or lower respiratory tract involvement. Their use will be described under complications of the common cold. In fact, the promiscuous routine use of these drugs should be discouraged for they fail to alter the clinical course and in addition they carry with them some danger of toxic reactions and the possibility of producing an allergic state.

Use of the Antihistaminic Drugs
The antihistaminic drugs have gained some popularity particularly among the laity as an aid in aborting the common cold. Results are dubious. Pyribenzamine benadryl neoantergan thephorin and histadyl are a few of the many antihistaminic drugs available. The prescribed dose varies from 25 or 50 mg. three or four times a day given at the onset of the cold and continued for 2 days. These drugs may be of value in those individuals with an allergic rhinitis or in those allergic individuals whose symptoms are accentuated by the upper respiratory infection. The side reactions associated with their use such as sleepiness vertigo weakness drowsiness cerebral stimulation insomnia and tremors make their use limited. Individuals operating machines or vehicles engaged in dangerous occupations or responsible for the safety of others should avoid the use of these drugs.

Treatment of Complications SINUSITIS
The sinuses may become involved during an attack of the common cold by secondary bacterial invasion or by the result of inadequate drainage. If drainage is adequate acute sinusitis will usually subside spontaneously and treatment is directed to relief of local symptoms and to the control of the infectious process. Bed rest in a warm moist room for the duration of the acute process is necessary. Steam plain or medicated is valuable in humidifying the room. The facial or frontal pain may be relieved by aspirin 10 or 15 grains (0.6 or 1 gm.) codeine $\frac{1}{4}$ or $\frac{1}{2}$ grain (15 or 30 mg.) and/or heat moist or dry applied over the involved sinuses. To pro-

mote drainage vasoconstrictor nose drops sprays or tampons (1 per cent ephedrine sulfate 0.25 per cent neosynephrine hydrochloride 10 per cent pramine hydrochloride and 10 per cent tuamine sulfate) are beneficial. Slight negative suction will further promote drainage. The response in many patients to penicillin treatment is most dramatic. Aqueous procaine penicillin 300 000 or 400 000 units given intramuscularly every 24 hours will often abort the condition prevent further spread of the infection and markedly reduce the need for surgical intervention. Aqueous penicillin 50 000 units every 3 hours is also effective. Penicillin is also beneficial when administered by aerosol or in dust form. 50 000 units of penicillin per cubic centimeter administered four or five times a day is a valuable form of treatment. The Vaponefrin Company supplies an atomizer which delivers a fine spray of penicillin and offers a suitable and simple method of disseminating penicillin to the sinuses. Abbott Laboratories also supply a simple portable plastic aerohelator for nasal and oral inhalation which dispenses 100 000 units of penicillin dust. Dosage varies from 100 000 to 300 000 units a day. In resistant cases rather than attempt further medical care consultation with an otolaryngologist should be obtained.

OTITIS MEDIA
Not infrequently the individual with the common cold develops otitis media. Most of the infections are the result of pneumococcal and streptococcal invasion of the middle ear and are amenable to penicillin and sulfonamide treatment. Intramuscular aqueous procaine penicillin 300 000 or 400 000 units every 24 hours and intramuscular aqueous penicillin 50 000 units every 3 hours are specifics. Equally beneficial although on rare occasions producing severe drug reactions is sulfadiazine 0.5 or 1.0 gm. every 4 hours with an equal amount of sodium bicarbonate. Heat by means of a hot pad or a well covered hot water bottle to the ear aids in relieving pain. Analgesic ear drops are important in the early stages of the otitis media. Three to 5 drops of auralgan (Doho) or 1 per cent phenol in glycerin dropped in the ear every 2 or 3 hours will relieve pain. Fortunately penicillin and the sulfonamides usually prevent an increase in the amount of pus but if bulging occurs

paracentesis under local or general anesthesia becomes necessary. Any further spread of infection with the development of mastoiditis or lateral sinus thrombosis demands specialized surgical intervention.

LARYNGITIS When laryngitis develops the management as described for the common cold should be rigidly continued. The patient is instructed to rest, not to speak or whisper. Smoking is prohibited. It is advisable to avoid atropine and opiates of all forms for they decrease secretion which is desired. Penicillin, aureomycin and the sulfonamides are of no value. No local treatment is necessary.

BRONCHITIS This is one of the more frequent complications of the common cold. Fatigue, exposure, chilling and allergy seem to predispose to its development. The patient must remain in bed until the temperature has been normal for at least 2 days. Smoking should be avoided. Fluids to 3000 cc a day are continued as during the period of the acute cold. Steam inhalation is of utmost benefit. Symptomatic relief of headache is accomplished by prescribing codeine $\frac{1}{4}$ or $\frac{1}{2}$ grain (15 or 30 mg) or empirin compound with codeine $\frac{1}{4}$ grain or aspirin 10 or 15 grains (0.6 or 1.0 gm) every 4 hours. Penicillin is the antibiotic of choice if a pneumococcus or streptococcus is the secondary invader administered in doses of 300,000 or 400,000 units of aqueous procaine penicillin once or twice a day depending on the severity of the infection. Aqueous penicillin 50,000 units every 3 hours is also used. In many patients no specific organism is isolated. In such cases aureomycin is more desirable than penicillin. Its recommended dose is 1 gm four times a day until symptoms regress, then 250 mg four times a day. Reduction in the dose of aureomycin often becomes necessary because of the nausea, vomiting or diarrhea it may induce.

Vaccines Mixed bacterial vaccines given orally or parenterally have been disappointing in their result and their use is not to be encouraged.

Vitamins Polyvitamins or specific vitamins offer no specific prevention. Their value is limited to individuals who develop protracted colds and show signs of nutritional deficiencies.

Sulfonamides and Antibiotics These agents have been tried as preventives for the common cold but results are extremely disappointing. Sulfadiazine has had clinical trials and will not affect the course of the common cold and should be restricted to specific complications. The same holds true for mass prophylaxis with penicillin.

Prevention Isolation of the patient and avoidance of contact is essential in preventing the spread of the common cold. Control of atmosphere, ultraviolet irradiation, dust control measures and the use of glycol vapors have been shown to be effective in reducing the spread and incidence of respiratory diseases. The disinfection of air by these means necessitates specialized equipment which may in the future be utilized in the construction of buildings and hospitals.

RENO ROSE

INFLUENZA

Recent advances in viral studies have shown the specificity of influenza and one must consider the term as applied solely to the disease produced by influenza viruses, types A and B. It is characterized clinically by severe constitutional symptoms of fever, chills, headache, prostration, muscular aching and cough. Symptoms and severity vary with each particular outbreak.

Prevention With the increasing knowledge of the cause and spread of influenza, there have been added impetus and advancement in the attempt to control and eventually to eradicate the disease.

Experimental and clinical evidence has shown that the virus of influenza is primarily air-borne. With this evidence there have been attempts to control the atmosphere by means of chemicals (glycol vapors) or ultraviolet irradiation. Methods of utilizing these agents are still experimental. Equipment is complicated and now rests in the hands of architects working with clinicians designing buildings and hospitals for the future.

Immunization against Influenza Two methods of immunization have been employed, namely producing active immunity with influenza vaccine and supplying passive immunity by serum. The latter has shown to be of no value in preventive therapy. So mordinetseff et al have reported excellent

protection in man by the intranasal spraying with high titered immune sera prepared from horses. This has not been corroborated by other investigators.

In contrast to the use of serum the subcutaneous injection of influenza types A and B vaccine has been shown to be effective in producing active immunity. It appears that vaccination will probably be valuable in preventing epidemics if an adequate potent vaccine is available and is given to large enough numbers of people. Studies carried out under the control of the Commission on Influenza of the United States Army Epidemiological Board showed that vaccination produced a protective effect of short duration. The vaccine used by this group consisted of a suspension of formalin inactivated influenza viruses of representative strains of types A and B. A single injection of 1 cc was given subcutaneously. In 1943-44 12,500 ASTP students were studied in each study alternate individuals receiving virus vaccine the others a control injection. Results showed that 71 per cent of the unvaccinated and 22 per cent of the vaccinated groups were hospitalized for influenza. Other studies have substantiated these findings. The success of influenza vaccine rests on the premise that the disease must involve an etiologic strain or strains which is similar to the strain or strains contained in the vaccine.

Influenza virus vaccine containing both types A and B viruses is prepared from allantoic fluid of chick embryos injected with various strains of influenza virus types A and B. Inactivation is produced by formalin.

Dosage. The recommended dose for adults is one injection of 1.0 cc subcutaneously and for children two 0.5 cc injections 7 days apart. The duration of immunity following this dose is not known and if unusual epidemic conditions prevail it seems a good policy to repeat a dose of 0.5 cc. A booster injection is advisable 11 to 12 months after the basic immunization. The unfavorable results to influenza vaccine are those of local soreness, erythema and systemic manifestations of chills, fever and muscular aching.

In unusual instances fatal anaphylactic shock has been reported. In persons known to be sensitive to eggs or chicken feathers it is wise to proceed with caution and a pre-

liminary skin test dose of 0.01 cc. of the undiluted vaccine should be given.

INDICATIONS FOR VACCINATION. Vaccination of whole populations against influenza seems inadvisable. It is better to concentrate on those who are susceptible to protracted respiratory infections and on those groups in which one desires to reduce time loss from their work. In the latter group students in industrial workers, hospital personnel and the military are particularly important to immunize.

Active Treatment. No specific treatment is available. Bed rest and the judicious use of chemotherapeutic agents and antibiotics are necessary. Bed rest is imperative and should be continued throughout the febrile period and the first 3 to 4 days of convalescence. The diet should be varied to suit the individual's desire, preferably liquid to soft. The fluids ingested should total 3000 to 4000 cc a day. In general the management of the patient with the common cold pertains to influenza. Acetylsalicylic acid 5 or 10 grains (0.3 to 0.6 gm.) empirical compound with codeine 1/4 grain and codeine 1/4 or 1/2 grain (15 to 30 mg.) will usually relieve the generalized aching and headache. A warm humid atmosphere is desirable.

The sulfonamides, penicillin and aureomycin are frequently prescribed since influenza predisposes to invasion of the respiratory tract by secondary organisms such as streptococci, pneumococci, and staphylococci. They have no specific action on the influenza virus but have a decided effect on the secondary invaders. In most cases they are not used unless complicating signs appear. Sulfadiazine 15 grains (1.0 gm.) with an equal amount of soda bicarbonate every 4 hours, sulfonamide mixtures (sulfathiazole, sulfadiazine, sulfamerazine) (1.0 gm.) every 4 hours are frequently used. Penicillin is also effective in controlling complications when administered intramuscularly in aqueous solution 50,000 units every 3 hours or as aqueous procaine penicillin 300,000 or 400,000 units daily. Aureomycin has been used with some apparent benefit in atypical pneumonia and although its use in influenza has not been established, it holds promise. The recommended oral dose has not been determined but 1.0 gm. four

times a day until symptoms regress followed by 500 mg four times a day seems to be adequate

RENO ROSE

REFERENCES

- Bresler H R Incidence of Reactions to New Type of Influenza Virus Vaccine in Industry *Indust Med* 16 301 1947
- Curphey T J Fatal Allergic Reaction Due to Influenza Vaccine *JAMA* 133 106° 1947
- Francis T Jr Transmission of Influenza by Filtrable Virus *Science* 80 457 1934
- Henle W and Zellat J Effect of Propylene Glycol Aerosol on Air borne Virus of Influenza A *Proc Soc Exper Biol & Med* 48 544 1941
- Henle W Sommer H E and Stokes J Jr Studies on Air borne Infection in Hospital Ward Effects of Ultraviolet Irradiation and Propylene Glycol Vaporization Upon Prevention of Experimental Air borne Infection of Mice by Droplet Nuclei *J Pediat* 21 577 1942
- Hirst G K Agglutination of Red Cells by Allantose Fluid of Chick Embryos Infected with Influenza Virus *Science* 94°° 1941
- Parker F Jr et al Pathologic Findings in Lungs of 5 Cases from which Influenza Virus was Isolated *Am J Pathol* 9°° 97 1946
- Robertson O H et al Sterilization of Air by Certain Glycols Employed as Aerosols *Science* 93 213 1941
- Silk J E and Francis T Jr Immunization Against Influenza *Ann Int Med* 25 443 1946
- Smorodintzev A A Gulamow A G and Tschalkina O M Über die spezifische Prophylaxe der epidemischen Grippe durch Inhalation antigruppösen Serums *Ztschr f klin Med* 138 756 1940
- Smith W Andrewes C H and Laidlaw P P Virus Obtained from Influenza Patients *Lancet* 2 66 1933
- Van Gelder D W Greenspan F S and Dufresne N E Influenza Vaccination Comparison of Intracutaneous and Subcutaneous Methods *U S Nav M Bull* 47 197 1947
- Wells W F and Henle W Experimental Air borne Disease Quantitative Inoculation by Inhalation of Influenza Virus *Proc Soc Exper Biol & Med* 48 298 1941

PSITTACOSIS

Psittacosis an elementary body disease caused by the viral agent *Miyagawanella* is to add with increasing frequency

established the fact that pigeons sea gulls doves ducks and chickens are infected and contribute to human illness. Petrels on the Faroe Islands and in Iceland are reservoirs of the virus. Human psittacosis has repeatedly been traced to canaries and some finches. The disease sometimes erupts in house epidemics and study of some of these has revealed many of its characteristics (Meyer Meyer and Eddie)

In recording the history of a patient under observation for possible psittacosis infection it is important to note whether or not he has had contact however slight with the birds or mammals which may be reservoirs. As in all heterogenous infection chains the element of chance here plays a role and fleeting exposure sometimes escapes notice. The diagnostician must constantly bear in mind that despite the designation of "psittacosis" or the implication of the term "parrot disease" any species of bird particularly those enjoyed by fanciers must be suspected as a source of pneumonitis.

Prevention GENERAL MEASURES The deep seated love for birds and in some instances their economic value make it useless to preach as a paramount prophylactic measure that parakeets lovebirds pigeons chickens ducks and other birds be excluded from human dwellings and their surround

to create and to maintain a bird industry free from psittacosis. Their efforts have been thwarted because the majority of owners and breeders cannot be convinced that the disease exists and is of real danger to human beings and they do not follow instructions or obey the simple rules of prevention. Consequently, health officers of many states and United States territories found it necessary with the rising incidence of the disease to request modification of the Interstate Quarantine Regulations the recommended laws became effective in June 1947. They specify that no person shall offer psittacine birds for transportation or transport such birds in interstate traffic unless owners accompany the shipment, and the shipment must not exceed 2 birds. No sanitation program has been instituted to reduce risks from or ducks

lovebirds have contributed to its spread. Furthermore overwhelming evidence has es

ACTIVE IMMUNIZATION Since Rivers and Schwentker in 1934 actively immunized several laboratory workers with living virus the possible danger of creating the carrier state by this method has been recognized and it has never been used even to protect laboratory workers or bird dealers. Lately phenol killed ether extracted yolk sac suspensions of virus elementary bodies have been employed in several laboratories for the protection of personnel (Wagner et al.) but the value of these protective inoculations has not been determined.

PROPHYLACTIC MEASURES AGAINST HUMAN TO HUMAN INFECTION The infectivity of the psittacosis virus is well known. Human to human infections have been observed and proved. In at least 23 instances involving 30 nurses the disease developed after exposure to infected persons and contact with diseased birds was definitely excluded. Of particular interest is the fact that nurses or attendants may become infected and in turn may transmit virus to others. In the experiences of Eaton, Beck, and Pearson the infection spread from one man to 3 nurses. In the 1943 epidemic of severe pneumonitis in the Bayou region of Louisiana the death of 8 nursing attendants exposed to a patient 48 hours before death and the illness of 11 others emphasize the importance of direct contact in human to human transmission (Olson and Treuting). Statistics such as these should serve to remind physicians that the occupational hazard to themselves and to nurses is considerable. The instances described and others of the past indicate that the sputum of human beings may harbor the agent of psittacosis. No definite rules can be given as to the period of quarantine. In any event it is imperative that disinfection and disposal of buccal discharges be carefully supervised. For their protection nurses should wear rubber gloves and cellophane masks. The virus resists desiccation and is readily dispersed in the air in droplets; projectile coughing heavily contaminates the environment. Patients should be confined in isolation rooms having minimal air currents and protective measures designed to prevent escape of air into wards and halls of the hospital. The experiences reported by Louzaga and Auerbach in a hospital in Buenos Aires attest to the risks involved when pa-

tients with unrecognized psittacosis are cared for in open wards.

Treatment **TREATMENT OF THE ATTACK** In principle symptomatic treatment and nursing should follow procedures now used in typhoid. The convalescent patient should be carefully watched in the majority of cases resolution is slow and relapses have been observed.

SYMPTOMATIC TREATMENT Proper nourishment is quite important and frequent small feedings are indicated. Fluids should be given freely and in adults the intake should be kept at 3000 to 4000 cc per day. Tepid sponge baths to reduce temperature are all ways indicated. Efforts should be made to improve the patient's well being. An ice cap may make him more comfortable and some times is efficacious in decreasing fever. The delirious patient of course requires particular attention since in his delirium he may get out of bed and injure himself. Insomnia may be treated with 0.1 gm of secenal. To relieve the constipation which sometimes troubles some mineral oil or citrate of magnesium may be used although soapsuds enemas are recommended. Codeine (30 mg) is the most useful drug for treating headache. Cough is rarely of importance; expectorant drugs should be administered only when a specimen of sputum is desired for laboratory diagnosis.

CONVALESCENT SERUM TREATMENT Between 1930 and 1944 treatment with convalescent serum was used in 11 cases.

dose was from 50 to 100 cc and was administered intramuscularly or intravenously. From the limited reports available it is difficult to judge objectively the value of this therapy.

CHEMOTHERAPY As early as 1930 Brink-

applied supportive evidence of its efficacy after tests in mice. Their observations have not since been further confirmed nor has the drug been employed in any large series of human infections. More recently (1948) Hurst demonstrated that "nitroakridin 3582" (Hochst) or 2, 3-dimethoxy-6-nitro-9 (3-diethylamino-2-hydroxypropyl) amino-acri-

dmedihydrochloride possesses moderate therapeutic activity against the viral agent of psittacosis in mice

Sulfonamides Early experiments by Rudd and Burnet and unpublished observations of Eddie and Meyer offered no proof that any of the sulfonamide compounds are of any value against the majority of known strains of the psittacosis virus. With the strains of virus at the disposal of Hurst, sulfadiazine and sulfamezathine constantly failed to prevent death in mice and usually prolonged but slightly the mean period of survival. Biehl and Heinlein claimed that sulfamyl urea was curative in some experiments. Meiklejohn et al and Early and Morgan found sulfadiazine effective against two classical psittacosis strains (6BC and Gleason). These observations may in part explain the clinical cure reported by Hinshaw. In view of the greater effectiveness of penicillin on all strains thus far tested, there is no need to resort to sulfonamide therapy in psittacosis.

PENICILLIN Heilman and Herrell, Bedson and May, Meiklejohn et al, Wiseman et al, and Early and Morgan studied the effect of penicillin on experimental psittacosis in the mouse and found it to be highly favorable. Workers at the Hooper Foundation (Meyer, Eddie, and Quan), treating experimentally infected mice and ricebirds, obtained convincing therapeutic results when treatment was instituted early in the course of the infection, and the antibiotic was used in large doses. Ricebirds often relapsed and died 22 to 27 days after discontinuation of intensive treatment (8,000,000 units over a period of 17 days). Penicillin has also been found to have a definite effect on the course of the disease induced in chick embryos by the viruses of psittacosis and of meningopneumonitis (Parker and Diefendorf). To maintain comparable concentrations in man, however, would require the daily injection of millions of units of penicillin. In view of these experimental studies, it was argued that penicillin in all probability would be ineffective in therapy of human psittacosis. Using the chick embryo testing technique, Eaton et al experimented with the murine, feline, and meningopneumonitis viruses and likewise concluded that these agents were relatively insusceptible to penicillin. The favorable clinical results reported, on the other hand,

have invalidated the early conclusions. Turgasen was the first to report on the apparently favorable effect of penicillin in a case of psittacosis. Treatment was instituted on the eighth day of illness and consisted of an injection of 100,000 units per day. On the third day the temperature was normal. A similar result was noted by Flippin, Gaydosch, and Fittipaldi, although penicillin therapy was not instituted until the 19th day of illness. Parker reported recovery of patients 61 and 52 years of age, respectively, whose psitta

1
6
fifth and seventh hospital days, respectively. The temperature of one patient dropped from 104.5° to 98.6° F on the second day of the penicillin treatment, but continued to fluctuate for several days between 98.6° and 101.4° F. A normal temperature was reached by lysis on the 11th hospital day (15th day of the illness) in a second case. Recovery followed promptly after institution of penicillin therapy on the 10th day of illness with 520,000 units in the case reported by Kulkwood. In the laboratory infection described by Rosebury and collaborators the dramatic resolution of symptoms followed combined therapy with penicillin and sulfadiazine which was begun on the fourth day of the illness. The strain of the psittacosis virus which caused the infection responded favorably to either therapeutic agent. Rosebury et al expressed the view that the combined therapy and the patient's previous vaccination were responsible for the good results.

Through the courtesies of the attending physicians, Meyer and Eddie (unpublished observations) had occasion to review over a period of 3 years the histories of 68 psittacosis patients who had received penicillin in the course of their treatment. The clinical diagnosis had been confirmed through serologic tests or isolations of the virus or both conducted in the laboratories of the Hooper Foundation. Most of the patients had received sulfonamides before penicillin was administered. Of the patients treated at different stages of the disease 4 or 5 per cent died, apparently as a result of inadequate therapy or undetermined complications. Whenever penicillin was given in large doses improvement was usually prompt and even

dramatic in several cases. In 6 laboratory infections proved to be psittacosis through isolation of virus from the sputum or blood or both the patients received penicillin as the sole therapeutic agent. The victims of the infection belonged to the age group of 25 to 55. The antibiotic was given parenterally in daily doses of from 80 000 to 320 000 units; total doses ranged from 980 000 to 3 190 000 units over a period of 10 days. The following observations are significant.

In one case of viremia in which the psittacosis agent was demonstrable in the sputum the condition responded promptly to a relatively small dose of from 80 000 to 160 000 units daily for 10 days; a total of 1 470 000 units although recovery was slow. Consequently in a later case with similar manifestations the dose was increased to 40 000 units every 3 hours or 320 000 units daily. Before treatment the course was toxic with marked malaise, severe headache and remittent fever (with swings from 99.8° to 101.0°).

matic and clinical improvement began 48 hours after initiation of specific treatment. The patient was afebrile on and after the 4th day.

days

These observations pointed the way for subsequent treatment schedules in psittacosis. Daily doses of not less than 300 000 units and a total dose of from 2 600 000 to 3 200 000 units over a period of about 10 days are now employed. Large initial doses (up to 100 000 units every 4 hours) are particularly recommended if diagnosis has been delayed and treatment initiated late.

It is not surprising to recall that crystalline penicillin G proved ineffective in the treatment of 3 human infections while aureomycin established cures. Studies on the dynamics of penicillin suggest that this antibiotic acts on the extracellular phase of the viral agent when it is not actually multiplying. Whenever the immunity mechanism is sluggish or impaired by toxins penicillin treatment must be prolonged until the

antibodies of the host are capable of taking over the bacteriostatic and bactericidal effects of the antibiotic. How far the multiplication within the host cells may be inhibited by penicillin is not known. Experiments on mice and the observations on one human psittacosis virus carrier failed to furnish much encouragement. Over 10 000 000 units administered parenterally or by inhalation exerted no effect on the localized respiratory infection of the human carrier. The virus was again isolated from the sputum several weeks after treatment had been discontinued. Early and intensive treatment of the infections reduces the number of viral elements and permits the normal body defense mechanism to dispose of the few stragglers. The serum of several patients treated with penicillin was again examined 6 to 12 months after the first studies and invariably the complement fixation titer had dropped to 1:2 or 1:4. Thus in the light of previous experience rather definitely indicates complete autosterilization and freedom from viral elements.

The introduction of penicillin has enriched the therapy of psittacosis. Adherence to the suggestions outlined will reduce the number of carriers, prevent the development of the carrier state and diminish the unduly high human fatality rate (20 per cent).

It is not unlikely that aureomycin (or chloramphenicol) may replace penicillin. Preliminary trials with 5 to 20 mg per kilogram of body weight have yielded encouraging results in infected mice and birds. Daily doses for intramuscular injection should range from 0.5 to 1.0 gm. The drug may also be given orally in doses of 2 to 4 gm daily.

KARL F. MEYER

REFERENCES

1. C. D. J. A. M. 1941. —

1941-42 1941

* The importance of aureomycin and chloramphenicol as possible potent therapeutic agents in psittacosis cannot be overemphasized. Woodward has recently pointed out the effectiveness of both antibiotics in patients infected with the agents of psittacosis and lymphogranuloma venereum. Herrell has also indicated the usefulness of aureomycin in psittacosis.—Editor

Virus from Cases of Atypical Pneumonia, Rela-

- cillin *JAMA*, 128 280 1945
- Hegler, C Psittakose *Deutsche med Wchnschr*, 56 148, 1930
- Heilman, F R, and Herrell W E Penicillin in Treatment of Experimental Ornithosis *Proc Staff Meet, Mayo Clin*, 19 57, 1944
- Heilman, F R, and Herrell W E Penicillin in Treatment of Experimental Psittacosis *Proc Staff Meet, Mayo Clin*, 19 204, 1944
- Herrell, W E Observations on Clinical Use of Aureomycin *Proc Staff Meet, Mayo Clin*, 24 612, 1949
- Hinshaw, H C Psittacosis Possible Response to Sulfapyridine *Proc Staff Meet, Mayo Clin*, 15 657, 1940
- Hurst, E W Nitroakndin 3582 A Compound Possessing Chemotherapeutic Activity Against the Viruses of Psittacosis and Lymphogranuloma Venereum *Brit J Pharmacol*, 3 181, 1948
- Kirkwood T Human Ornithosis, Report of Case Treated with Penicillin *Illinois M J*, 90 193 1946
- Lozaga, N S, and Auerbach S Sobre una epidemia de psittacosis Predominio del contagio in terhumano *La Revista de medicina y ciencias afines* 7 297, 379, 461 543 1945
- Mauer, G Die Wirkung des Trypaflavins bei psittakoseinfizierten Mäusen *Zentralbl f Bakt (Abt 1)*, 142 279, 1933
- Meiklejohn G, Wagner, J C, and Beveridge G

M

- (De Lamar Lecture), *Memorie*, 24 115, 1929
- Meyer, A F, and Eddie B Knowledge of Human Virus Infections of Animal Origin *JAMA*, 133 822, 1947
- Meyer, K F, and Eddie, B Psittacosis in Importations of Psittacine Birds from South American and Australian Continent *J Infect Dis*, 65 234 1939
- Meyer, K. F., Eddie, B., and Quan, S F Unpublished Data
- Olson B J, and Treuting, W L Epidemic of Severe Pneumonitis in Bayou Region of Louisiana, Epidemiological Study *Pub Health Rep*, 59 1299, 1944
- Parker, R F Psittacosis as Cause of Atypical Pneumonia, Penicillin Therapy *Ohio State M J*, 41 1097, 1945

- Parker, R F, and Diefendorf, H W Effect of Penicillin on Certain Viruses *Proc Soc Exper Biol & Med*, 57 351, 1944
- Rivers, T M, and Schwenker, F F Vaccination of Monkeys and Laboratory Workers Against Psittacosis *J Exper Med*, 60 211, 1934
- Rosebury, T, Ellingson, H V, and Meiklejohn G Laboratory Infection with Psittacosis Virus Treated with Penicillin and Sulfadiazine, and Experimental Data Bearing on Mode of Infection *J Infect Dis*, 80 64, 1947
- Rudd, C V and Burnet, F M Intranasal Infection of Mice with Virus of Psittacosis *Australian J Exper Biol & M Sc*, 19 33, 1941
- Turgason F. E Human Ornithosis Treated with Penicillin *JAMA*, 126 1150, 1944
- Wagner, J C, et al Psittacosis Vaccines Prepared from Chick Embryo Tissues *J Immunol*, 54 35 1946
- Wiseman, R W, et al Studies on Chemotherapy of Viruses in the Psittacosis Lymphogranuloma Group, Effect of Penicillin and Sulfadiazine on 7 Strains in Mice *J Immunol*, 54 9, 1946
- Woodward, T F Chloromycetin and Aureomycin *Ann Int Med*, 31 53, 1949

HERPES ZOSTER

Herpes zoster is an acute virus infection of the dorsal root ganglia or extramedullary ganglia of the cranial nerves with secondary involvement of the skin Typically, the clinical picture is ushered in with the sudden appearance of tense vesicles surrounded by a zone of erythema, along the skin segment supplied with sensory nerves of the ganglion or ganglia involved The pain is intense, burning, constant, and radiates along the affected root It is resistant to treatment and may last weeks to years Hyperesthesia of the involved skin segment is usually present Motor weakness may be associated with the sensory change Herpes of the ophthalmic division of the trigeminal nerve may be serious because of ocular complication Central nervous system involvement has been reported and spinal fluid examination in these patients reveals a pleocytosis

Local Treatment Local treatment is directed primarily to protecting the lesions from infection and trauma and to the relief of pain and itching Ordinary dusting powders of equal parts of zinc stearate, starch and talc, or of thymol iodide, are applied three times a day to the involved areas which are then covered with thick pads of

absorbent cotton. If the vesicles are unruptured collodion may be painted over the affected site. Carbonized calomine lotion (1 per cent phenol) in generous application three or four times a day is helpful for its soothing effect. Seventy per cent alcohol applied locally and covered with abundant loose cotton batting will protect the hyperesthetic areas. When irritation of the skin develops wet dressings of Burow's solution (1:10) are of value.

The number of therapeutic agents recommended for relief of pain of herpes zoster is an indication of the lack of specificity of any one of these agents. Deep roentgen therapy directed over the involved ganglia 200 to 800 r daily for 4 to 6 days is frequently successful. Spraying of the involved skin with ethyl chloride gives temporary relief but has not been effective in producing complete relief. In the more severe cases paravertebral block gives excellent results. Ten cubic centimeters of 0.5 or 1.0 per cent procaine solution is injected with a No. 22 spinal needle

through an area of infected vesicles. This treatment is of great value in the hands of those competent enough to perform this type of block. When carried out within the first 72 hours of the infection results are excellent. The longer the disease has progressed before injection the less striking is the result. In older individuals paravertebral block does not afford as much pain relief. Thiamine hydrochloride 100 mg. injected into and beneath the area of eruption has been advocated but results are inadequate.

Relief of Pain by Drugs. In many patients local treatment fails to relieve the persistent agonizing pain of herpes zoster and analgesic drugs and opiates must be used. Sodium salicylate 15 or 20 grains (1.0 or 1.3 gm.) four times a day or 2 tablets of empirin compound four times a day will lessen the pain. When these fail one may resort to codeine $\frac{1}{4}$ to 1 grain (15 to 60 mg.) every 4 hours. Morphine sulfate $\frac{1}{8}$ grain dilaudid $\frac{1}{4}$ grain and demerol hydrochloride 50 or 100 mg. are used only in rare cases of prolonged and unbearable pain. Pituitrin 0.5 or 1.0 cc. intramuscularly every 24 hours for 3 or 4 days is also used. Its use

is contraindicated in pregnancy, hypertension and cardiac disease. A striking relief from pain is often obtained by the daily intravenous injection of 1 or 2 gm. of sodium iodide given during the acute phase of the disease until the pain subsides. The danger

50 or 100 mg. of thiamine. Diphtheria antitoxin 5000 units intramuscularly has been used but there is little justification for its administration. The possibility of anaphylaxis and serum reaction in sensitive individuals makes its administration dangerous. Bena-dryl 25 or 50 mg. four times a day for 5 or 6 days affords some patients relief but results are inconsistent. The same results are obtained with other antihistaminic drugs such as pyribenzamine, neoantergan, theophyllin and others.

Reports on observations of the use of aureomycin in relief of herpes pain have been most encouraging. Frequently its action is

hours for 3 or 4 days is adequate. Although further studies are necessary, early reports indicate that aureomycin may be the drug of choice in this disease. The value of chloromycetin is not known.

RENO ROST

MEASLES

Measles is an acute infectious, highly communicable disease of universal distribution characterized by prodromal catarrhal symp-

agent

Prophylaxis. Public health measures for the control of measles are generally ineffective. Any susceptible individual who is exposed to the disease is likely to develop it. It is highly contagious in the prodromal period which accounts to a great extent for the rapidity of its spread. The contagion is lessened after the rash has reached its peak. Most health departments require isolation for a period of 7 to 10 days after onset of the rash. Children under the age of 10 years who have had direct contact should be placed

under quarantine for a period of 14 days from the day of exposure. Adults are not restricted in their activity.

There are now specifics available which are effective in preventing or modifying measles in contacts. In general, it is preferable to modify rather than prevent, in order that the individual may develop his own active immunity and thus be rendered immune to future exposures. Under certain conditions, however, prevention is best; these include (1) children under 3 years of age, an age group in which the mortality is highest, (2) children who have other acute or chronic disease, (3) children in hospital wards, and (4) susceptible women in the first trimester of pregnancy.

Convalescent serum, immune gamma globulin, placental extract, and adult human serum are effective in preventing or modifying measles. Of these convalescent serum and immune gamma globulin have gained the greatest favor. These agents if used for prevention produce a transient passive immunity, lasting up to a month, and will prevent measles only within that period. Convalescent serum is available at serum centers located in large urban areas. No standard dose is recommended but in general 10 to 20 cc given intramuscularly during the first 3 days following exposure will afford protection. The same amount given on the fourth to the eighth day after contact usually gives a modifying effect. After the eighth day the effect diminishes and is practically nil after the 11th day. Reactions are rarely seen. Although an effective agent in preventing and modifying measles, the use of convalescent serum is limited because of its relative scarce supply.

Since World War II, immune gamma globulin processed from pooled normal human plasma has been available and is more extensively used because it is more easily obtained than convalescent serum. Clinical trial has shown it to be as effective as any other protective or modifying agent. Immune gamma globulin is prepared so that each 10 cc contains 160 mg of gamma globulin. It is concentrated to a titer 25 times greater than in normal human plasma. For modification 30 to 37 mg of gamma globulin per pound of body weight should be administered intramuscularly during the

first 6 days of the incubation period. The dose of immune gamma globulin varies, depending on the effect desired, namely, prevention or modification, the age and weight of the person, and the day of the incubation period. The following intramuscular dose schedule is recommended for modification by the Cutter Laboratories:

Weight (lbs)	Total Dosage (cc)
15	0.3 to 0.4
20	0.4 to 0.5
25	0.5 to 0.6
30	0.6 to 0.7
35	0.7 to 0.8
40	0.8 to 0.9
45	0.9 to 1.0
50	1.0 to 1.2

For complete protection five times as much should be given early in the incubation period (15 mg or more of gamma globulin per pound of body weight).

Studies by Bundesen showed that there was little difference in results obtained by various prophylactic agents given before the fifth or sixth day. Top and Badger, however, revealed a marked improvement in result in giving injections during the first 3 days of the incubation period.

With the easy availability of immune gamma globulin, the need for adult human serum and placental extract has practically disappeared. Larger doses of adult serum are necessary, varying from 10 to 80 cc intramuscularly. Intramuscular placental extract is usually administered in 2 to 10 cc doses for prevention and 2.5 cc for modification. Local and systemic reactions of mild to moderate severity may occur.

It is well to remember that the diagnosis of modified measles may be difficult for there is a marked amelioration of signs and symptoms. The incubation period may be prolonged, the rash may be minimal, and the fever low grade or absent.

Active Treatment. The treatment of measles is symptomatic and no specific antibiotic or chemotherapeutic agent has been developed to reduce further the present low death rate. The patient should be isolated in a warm room. Rest in bed during the acute febrile period is imperative. The diet should be adequate, preferably liquid or soft.

warm boric acid solution. Warm compresses also aid in relieving conjunctival irritation. In patients with distressing symptoms resulting from upper respiratory involvement (laryngitis, tracheitis, bronchitis) relative high room temperatures and increase of humidity are a help. Steam inhalation, plain or medicated with menthol or tr of benzoin reduces the severity of cough. For the younger children a croup tent is a great help. Cough mixtures containing small amounts of codeine ($\frac{1}{2}$ to $\frac{1}{4}$ grain) (8 to 15 mg) to suppress the cough should be given. Suitable preparations are

		gm or cc
Codeine phosphate	gr iii	0.18
Eluxir terpin hydrate	fl oz iv	120.0

Sig 1 teaspoonful every 3 hours for cough

		gm or cc
Codeine phosphate	gr iv	0.24
Syr wild cherry	fl oz iv	120.0

Sig 1 teaspoonful every 3 or 4 hours for cough

Aspirin, 5 to 10 grains (0.3 to 0.6 gm), or aminopyrine, 5 grains (0.3 gm) three or four times a day, is effective in reducing high temperatures. Fevers not reduced by these antipyretics may be controlled by tepid water sponging or alcohol rubs. Sulfonamides and antibiotics are reserved for those cases in which complicating secondary infection occurs and the agent used depends on the invading organism. Sulfadiazine, 5 to 15 grains (0.3 to 1.0 gm), with an equal amount of sodium bicarbonate, every 4 hours, aqueous procaine penicillin, 400,000 units intra-

the difficulty in obtaining such large amounts of serum, plus the uncertainty of results, make its use unfeasible.

Frequent examination of the ears is essential. If otitis media has developed aqueous penicillin, 50,000 units intramuscularly every 3 hours, aqueous procaine penicillin, 300,000 or 400,000 units every 24 hours, or sulfadiazine, 5 to 15 grains (0.3 to 1.0 gm.) every 4 hours, is indicated and is usually effective. If ear pain is severe and the tympanic membrane is bulging, paracentesis may be necessary. Frequent examination of the mastoid in these patients is important.

The nose should be kept clean and comfortable. Vasoconstrictor drugs (0.5 to 1.0 per cent aqueous ephedrine sulfate, 0.25 per cent neosynephrine (SKF) solution) will frequently give relief from nasal obstruction. Only suspensions are contraindicated. Zinc oxide ointment or petrolatum applied to the

mands diligent supportive care. Oxygen by nasal catheter or tent is of great help. Convalescent serum, although of questionable value, should be administered, 100 to 300 cc. intravenously. Mild sedation is important, phenobarbital, $\frac{1}{4}$ to $\frac{1}{2}$ grain (7.5 to 30 mg), chloral hydrate, 5 or 10 grains (0.3 to 0.6 gm), and sodium bromide, 15 grains (1.0 gm), may be used to control irritability, delirium, marked restlessness, and convulsions. Maintenance of the patient's nutrition

gavage mixture may be made up of milk,

venous infusion of 5 or 10 per cent glucose in distilled water or normal saline, may be given to maintain adequate fluid intake at 3000 cc a day. In those patients showing shock, infusion of 500 cc. of normal human plasma may help. In selected cases transfusion of 300 to 500 cc. of whole blood to adults and 200 to 300 cc. to children may be necessary. If urinary retention occurs catheterization is necessary.

RENO ROSE

supportive measures and oxygen. Once the disease has manifested itself, intramuscular or intravenous convalescent serum appears to be of little or no value. The use of large doses, 500 cc or more, in the pre-eruptive stage has held some promise, but the cost,

REFERENCES

- Bundesen H N et al Clinical Use of Immune Human Placental Globulin in Chicago *JAMA* 115 104 1940
- Cutter Laboratory Circular on Immune Globulin
- Rake G and Shaffer M F Studies on Measles The Use of the Chorio-allantois of the Developing Chicken Embryo *J Immunol* 38 177 1940
- Top F H and Badger G F Measles in Detroit 1935 Protective Use of Measles Convalescent Serum *Am J Hyg Sect A* 33 9 1941

RUBELLA

(German Measles)

Rubella is a mild acute highly communicable disease resembling measles and scarlet fever. The etiologic agent is probably a filtrable virus although it has never been isolated. Characteristic occipital posterior auricular and posterior cervical adenopathy occurs.

Treatment Rubella is so mild that no treatment other than symptomatic measures is indicated. Bed rest is advisable during the febrile period which rarely lasts for more than 2 or 3 days. Fever is readily combated by acetylsalicylic acid 5 or 10 grains (0.3 or 0.6 gm) three times a day. A liberal fluid intake (3000 cc a day) is advised. The diet should be soft. The enlarged lymph nodes are rarely painful but should pain develop the application of cold compresses gives relief.

Prevention Reports have suggested that a relationship exists between the occurrence of rubella in the first trimester of pregnancy and congenital anomalies such as cataracts, congenital heart disease, deaf mutism and mental deficiency. Further statistical study regarding this relationship is essential. With this possible danger confronting the mother it appears that some means should be carried out to prevent her from contracting the disease. Immune gamma globulin should be given to all pregnant women exposed to the disease in spite of the fact that its efficacy has not been determined. The dose of gamma globulin has not been established but it should be large 10 to 15 cc intramuscularly if early in the incubation period and 15 to 20 cc if late. Some physicians have advised therapeutic abortion for those women who contract rubella in the early months of pregnancy, but there is no agreement among the

profession on this radical procedure. It is felt that the final decision on this phase of management must await further observation and the possibility of other factors in producing these deformities. It follows that the female patient who develops rubella early in life may be considered fortunate. Certainly young female children should not be given immune gamma globulin for prevention of rubella.

Isolation is carried out during the acute phase of the disease and the patient is excluded from activity for 7 days. Contacts are not quarantined.

RENO ROSE

MUMPS

Mumps is an acute infectious disease of man caused by a specific virus and characterized by swelling of one or more of the salivary glands usually the parotids. A decided tendency to involve the testes, ovaries, mammary glands, central nervous system and pancreas is noted. Its occurrence is universal and it is more prevalent during the winter and spring months. Its highest incidence is in the age group of 5 to 15 years but many adults contract the disease, particularly those crowded in schools, camps, barracks, ships, etc.

Treatment Bed rest with bathroom privileges for the febrile period and until disappearance of salivary gland swelling is the most important factor in the treatment of mumps. If the gland is extremely tender cold compresses may afford relief. In patients with high fever, nausea and vomiting fluids should be administered parenterally.

Intake by mouth should reach 2500 to 3000 cc a day. Solid food should be avoided during the period of acute salivary gland swelling because of the pain encountered in chewing. The liberal use of acetylsalicylic acid 5 or 10 grains (0.3 or 0.6 gm) or of empyrin compound with codeine 1/2 grain (15 mg), is useful in relieving pain and aching. Seconal 1 1/2 grains (0.1 gm), phenobarbital 1 grain (60 mg), and nembutal 1 1/2 grains (0.1 gm), are useful in relieving restlessness and promoting sleep. Atropine sulfate is of no value. About 1 per cent of

patients develop a painless presternal edema for which no treatment is necessary.

ORCHITIS Bed rest is considered to be important in the prevention of orchitis but there is not general agreement on this procedure. In young patients orchitis is uncommon and this may indicate that the inactive tests are resistant to infection with mumps virus. On this theory diethylstilbesterol which inhibits testicular function is prescribed Prophylactically 2 mg of diethylstilbesterol are given every morning. Therapeutically, diethylstilbesterol is valuable in reducing the severity and the duration of the acute orchitis. The dose is 5 mg given orally each morning until the orchitis subsides. Local treatment consists of (1) proper support usually by means of an adhesive bridge which relieves the discomfort produced by the weight of the enlarged inflamed testes (2) local application of an ice bag (3) acetylsalicylic acid 5 or 10 grains (0.3 or 0.6 gm) every 4 hours or codeine $\frac{1}{4}$ or $\frac{1}{2}$ grain (15 or 30 mg). Surgical treatment of mumps orchitis is generally not necessary but some physicians feel it is indicated for those patients with an enlarged hard painful testicle and persistent chills and fever. The procedure advocated is an incision through the tunica vaginalis and multiple incisions of the tunica albuginea. The release of fluid by incision brings about relief of pain and usually lowers the temperature. The procedure necessitates gas anesthesia. Surgical intervention appears to be too radical and is not indicated in mild or moderate cases or in patients with a predominant epididymitis. The use of convalescent serum to prevent orchitis has a sound immunologic basis but is not practical. The dose is usually 40 to 50 cc given intravenously. Pooled normal plasma 100 to 200 cc intravenously has little effect in reducing the incidence of orchitis. Gellis gave 20 cc of gamma globulin prepared from mumps convalescent serum and reported excellent results. Gamma globulin prepared from normal plasma has no effect.

MENINGO-ENCEPHALITIS The symptoms of meningeal irritation, severe headache, stiff neck, nausea and vomiting, associated with an increase of lymphocytes in the spinal fluid is not uncommon in mumps. The prognosis is good. Lumbar puncture is performed

to establish the diagnosis and usually the amount of fluid removed is sufficient to relieve the severe headache. Multiple or daily spinal punctures are not advisable for the symptoms subside spontaneously or with the use of acetylsalicylic acid 10 or 15 grains (0.9 or 1.0 gm) or codeine $\frac{1}{4}$ grain (15 mg) given four times a day.

PANCREATITIS This complication is occasionally seen and is characterized by severe upper abdominal pain, nausea, vomiting and abdominal distention. Signs of ileus may be present. The serum amylase is markedly elevated. Treatment is conservative and it is imperative to recognize the condition as an acute nonsurgical condition of the abdomen. During the acute phase nothing is given by mouth and parenteral fluids (5 or 10 per cent glucose in normal saline and protein hydrolysate totaling 3000 cc a day) are given to maintain fluid balance. Codeine $\frac{1}{4}$ grain (30 mg), morphine sulfate $\frac{1}{4}$ grain (10 mg) or demerol hydrochloride 50 to 100 mg will usually relieve the abdominal pain.

MASTITIS This condition may occur in either sex but is uncommon. It requires no treatment other than the application of cold compresses to relieve the pain and swelling.

OOPHORITIS Oophoritis is much less frequent in females than orchitis is in males. It is essential to differentiate this condition from surgical abdominal lesions, particularly acute appendicitis. Treatment is conservative. Cold compresses applied to the involved side and the use of liberal amounts of aspirin will control the pain.

Prevention No practical method of active immunization is available in preventing mumps. The disease acquired before puberty is mild and mass prophylaxis is of little value. Convalescent serum 50 to 100 cc intravenously early in the incubation period will afford passive immunity and is recommended for adults who have been exposed and for seriously ill and debilitated children. Unfortunately, mumps convalescent serum is expensive and difficult to obtain. Gamma globulin is of no value. Stokes and his co-workers presented evidence that increased resistance could be produced in many children who received 10 cc of formalized mumps virus subcutaneously. The formalized vaccine had no effect when given during the incubation period of the disease.

Quarantine of the patient until the swelling of the salivary glands has subsided is advised. No restrictions are placed on adult contacts.

RENO ROSE

REFERENCES

- Gellis S S McGuinness A C and Peters M
Study on Prevention of Mumps Orchitis by
Gamma Globulin *Am J M S* 210 661 1945
Stokes J Jr et al Immunity in Mumps Experi-
ences on Vaccination of Human Beings with
Formolized Mumps Virus *J Exper Med* 84 407
1946
Wesselhoeft C and Vose B N Surgical Treatment
of Severe Orchitis in Mumps *New England J
Med* 277 277 1942

CHICKENPOX

(Varicella)

Chickenpox is a universal benign acute infectious highly communicable disease caused by a filtrable virus and characterized by mild systemic symptoms and a typical rash. When secondary infection of the skin eruption develops it may be difficult to differentiate from the pustular stage of smallpox.

Active Treatment Symptomatic treatment is the rule and efforts are directed to prevention of secondary infection. In most cases particularly children the disease is so mild it requires no treatment. Bed rest is advised during the febrile period. Fever is combated by the use of aspirin 5 or 10 grains (0.3 or 0.6 gm) given every 4 hours. The diet should be soft or light with ample quantities of liquids 2500 to 3000 cc a day. The itching is controlled by soothing lotions such as carbolyzed calomine lotion applied liberally to the skin twice a day. If a generalized pustular eruption occurs it is well to cleanse the skin with boric acid solution three or four times a day and apply wet dressings of potassium permanganate solution 1:5000 or Burow's solution 1:8. When crust formation has occurred 5 per cent sulfathiazole or sulfadiazine ointment may be applied. Careful attention to the hands and fingernails is important. The hands should be washed carefully with soap and water and the fingernails cut short to prevent scratching. In patients who are distressed unduly by the itching phenobarbital $\frac{1}{4}$ or $\frac{1}{2}$

grain (7.5 or 15 mg) four times a day should be prescribed.

The sulfonamides and antibiotics have no effect on the course of the disease but should be used if secondary infection of the skin occurs. Sulfadiazine 7.5 or 15 grains (0.5 to 1.0 gm) with equal amounts of sodium bicarbonate may be employed but its use has decreased considerably because of the specificity of penicillin. Intramuscular aqueous procaine penicillin 300,000 or 400,000 units once or twice a day controls the majority of secondary infections.

Central nervous system complications (meningitis, meningoencephalitis) are extremely rare and the prognosis is excellent. Headache is usually the only distressing symptom and is controlled by aspirin 5 or 10 grains (0.3 or 0.6 gm), every 3 or 4 hours. When convulsions and restlessness occur phenobarbital $\frac{1}{4}$ or $\frac{1}{2}$ grain (15 or 30 mg) chloral hydrate 10 grains (0.6 gm) three or four times a day should be prescribed.

Prevention Chickenpox is so mild in young children that no attempt is made to prevent the disease. Quarantine of the patient until the primary crusts have disappeared is essential. The prophylactic use of 2 to 3 cc of gamma globulin given intramuscularly during the incubation period or after exposure has been disappointing. Vaccination of individuals with vesicular fluid is not advised. The use of convalescent serum 15 or 20 cc intravenously, may aid in preventing or modifying the disease and should be administered to seriously ill or markedly debilitated children. It is not generally available.

RENO ROSE

SMALLPOX

(Varicella)

Preventive Treatment Smallpox vaccination in infancy with revaccination every 5 to 7 years and promptly before or after probable exposure have greatly decreased smallpox morbidity and mortality.

ISOLATION OF PATIENT Whenever possible the patient should be promptly transferred to the nearest isolation hospital where smallpox is treated. A special ambulance is desirable; the person transferring the patient should be vaccinated with potent vaccine.

before he comes in contact with the patient. The physician should have been recently vaccinated and should wear rubber gloves or use an aseptic hand technic to prevent the spread of the virus to susceptibles.

Specific Treatment The only specific treatment is prophylaxis by vaccination. Sulfonamides and penicillin are of value only in the prevention and treatment of the usual secondary streptococcal and staphylococcal infections.

General Treatment Good nursing care is of paramount importance. Sedation should be adequate to ease pain and lessen discomfort. At first, sponge baths twice daily with tepid water or aqueous zephuran chlo-

worst areas should be sprayed with aqueous zephuran chloride solution (1:1000) or repeatedly with a penicillin solution (10,000 units per cubic centimeter). Sulfathiazole as a dusting powder or ointment is applied to the most infected areas. The mouth is irrigated after each meal with tepid soda solution (1 teaspoon per 1000 cc).

The eyes require gentle, repeated care. Excess of pus is carefully wiped away with sterile gauze or cotton soaked with warm saturated boric acid solution. Then ophthalmic sulfathiazole, penicillin, or boric acid ointment is applied to the margin of each lid. These nursing measures are repeated six or more times both day and night. The ears and genital organs are treated in the same way if lesions there cause much discomfort. A glass drinking tube, rubber bulb, and drinking cup (with spout) are invaluable aids. The diet should include ample fluids and vitamins, 100 mg. of ascorbic acid daily is of value. Only when extensive and painful lesions in the mouth and throat prevent swallowing of adequate food and fluids should intravenous fluids and medication be used. They are otherwise contraindicated on account of the risk of blood stream infection. When the odor is especially repulsive, wet dressings of potassium permanganate solution (1:10,000) are applied and changed every 4 hours. Premature removal of scabs makes pitting more likely. A penicillin tablet (50,000 units) given by mouth every 3 hours

well tolerated and is safer than the muscular route.

Varioloid This modified form of smallpox occurs in patients who have been vaccinated earlier in life and who have since lost most of their immunity. The eruption usually appears after a 2 day prodromal period, the pustules are superficial and the lesions seldom terminate in scarring. The treatment is as outlined, but less frequently applied.

LOUIS W. SAUER

REFERENCES

- Smadel, J. E. Smallpox and Vaccinia in *Viral and Rickettsial Infections of Man*. Ed. by T. M. Rivers. Philadelphia: J. B. Lippincott Company, 1948.
- Stimson, P. H. Smallpox, in *A Manual of the Common Contagious Diseases*. Philadelphia: Lea & Febiger, 1947.
- Top, F. H. Smallpox in *Communicable Diseases*. St. Louis: C. V. Mosby Company, 1947.

SMALLPOX VACCINATION

(Vaccines)

Procedure Primary vaccination* is best administered to infants or young children during the first spring or autumn after completion of the other customary immunization procedures. The most approved technic both for primary vaccination and revaccination is the multiple pressure method because it is painless and highly successful. A secondary infection and disfiguring scar are far less likely to occur. The preferred site is the upper left arm at the depression caused by the deltoid insertion. The skin is cleansed with soap and water or wiped with a sterile swab of acetone or 70 per cent ethyl alcohol. After the skin is completely dry, the entire contents of one capillary is deposited at the site.

fingers above. The lower surface of the arm is

* Only fresh vaccine is used.

† A scar results from secondary infection, it is erroneous to assume it implies immunity.

held firmly with the left hand so that the skin at the vaccination site is stretched slightly. This facilitates penetration of the virus into the deeper layers where it then multiplies. The side of the needle point held at a sharp angle (almost parallel to the surface) is pressed firmly and rapidly with a perpendicular motion into the drop of vaccine—10 times in as many seconds for primary vaccination, 20 to 30 times for revaccinations. Only $\frac{1}{8}$ sq. in. should be involved. The site is then promptly but gently rubbed with the side of the needle tip to impregnate the virus further before the left hand is released. Excess of vaccine is wiped off with sterile cotton. If the inoculated area is kept limited the lesion and scar remain small. Trauma of the skin should be avoided; blood should not appear. The site need not be covered. Scratching might transfer virus to another surface and produce more lesions. If a sterile gauze dressing is applied to protect against scratching, it should be loose and is to be removed the following day. When the vaccination "takes" a shield should never be worn because the vesicle dries more rapidly with ventilation. Perspiration under a shield increases itching and a secondary infection is likely to result. The vesicle, which usually appears between the third and 10th days, is proof that a "take" has occurred.

Treatment of Lesion. During the first 10 days of a primary "take" the area should be kept dry. Water should not touch the skin there because maceration of the vesicular surface may rupture the lesion, permitting secondary invaders to gain entrance. Oozing of the contents should be avoided, as it increases the likelihood of secondary infection.

swelling and inflammation many physicians advise frequent dusting of the area with powdered boric acid (from a sifter top can) six to eight times daily. An accelerated reaction, a small vesicle within 2 days after

potent ("dead") vaccine may lead to a false interpretation of immunity.

If it is desirable to protect the vesicle for a few days a sterile gauze pad (3 by 4 in.) should be held in place with a narrow strip of adhesive across the top only (like an apron). This may be raised each time before the powdered boric acid is applied; the gauze should never adhere to the scab.

Revaccination. A previously vaccinated person may be immune without the presence of a visible scar. Many fatal cases of small pox have resulted from the erroneous assumption that the patient was immune when a revaccination did not "take" because an inert ("dead") vaccine was used. Revaccination may be performed at any time of the year and should be repeated every 5 to 7 years. If a prompt take or evidence of immunity is desirable, two vaccinations about 1 in. apart may be performed on both arms. The preferred site for revaccination is just above the old scar; if a scar is not found the vaccination should be repeated at the deltoid insertion of the left arm. The presence of keloid tissue in the vaccination scar usually disappears in the course of several years.

Complications. Secondary infection of the vaccination lesion is usually pyogenic. As a rule it responds to such simple measures as keeping the area dry with liberal repeated applications of powdered boric acid. Penicillin solution (10,000 units per cubic centimeter) may be sprayed from a nebulizer eight or more times daily. If improvement is not prompt, penicillin by mouth (50,000 units) every 3 hours for 3 days, or a daily intramuscular dose (300,000 units) for 2 or 3 days is beneficial. Secondary infection occasionally is due to tetanus. The familiar clinical symptoms, such as trismus and convulsions, should be recognized early. Previous routine immunization with tetanus toxoid (as in DTP) protects against this complication. Generalized vaccinia is likewise infrequent. When it is extensive, penicillin should be used both locally and internally. Post-vaccinal encephalitis is rarely encountered in this country. It is more likely to occur in individuals with central nervous system instability.

LOUIS W. SAUER

pustule formation. A traumatic reaction resulting from cross scratching or scarification may simulate an immune reaction. Use of im

REFERENCES

- Leake J. H. *Questions and Answers on Smallpox and Vaccination* Washington D.C. Government Printing Office, 1926
- Snader J. E. *Smallpox and Vaccines in Viral and Rickettsial Infections in Man* Ed by T. M. Rivers Philadelphia J. B. Lippincott 1918 Ch. XV

RABIES

Rabies is an acute infectious disease of lower animals caused by a neurotropic filterable virus. The virus is transmitted either from animal to animal or from animal to man by the introduction of infected saliva through the broken skin or intact mucous membrane. The disease is invariably fatal to man and to practically all warm blooded animals.

The treatment of rabies is so far entirely prophylactic. No patient known to have acquired the disease has survived. The elimination of the disease among animals and adequate prophylactic treatment in man must be our aim if we are to conquer the rabies problem.

Prevention of Rabies in Animals Regulation in England The British Isles is an outstanding example of a country in which rabies in animals has been prevented and regulated. Years ago it was recognized that the dog reservoir was the only important source of rabies in England. The care of dogs was regulated. It was required that animals be kept on their owners' premises or that they be effectively restrained by leash and/or muzzle when they were taken off the premises. Restrictions were placed on the shipping of dogs from one area to another and all dogs imported into the country were quarantined in isolation at the port of entry for 6 months in order to be sure that they were not in the incubation period of rabies. By these simple and sensible means the disease was completely eliminated and did not reappear in England until World War I when the import regulations program was relaxed and a few dogs were flown in from the Continent.

It would seem the best way to eliminate rabies in the United States would be to follow the practice of those countries which have successfully controlled the problem.

IMMUNIZATION OF ANIMALS In addition to the regulation and care of animals, there is now available a means of actively immunizing an animal against the disease. However more than a single dose of vaccine should be required for vaccination. It is difficult to justify the belief that a single dose of rabies vaccine given once a year to the average dog will produce solid immunity when it is common knowledge that we must give a human being 14 to 21 doses of vaccine to prevent the disease. The contribution of such men as Webster and Casals of the Rockefeller Institute and of Habel of the United States Public Health Service would indicate that single dose vaccinations are at best only partially effective. Much of the vaccine that was used until recent years was demonstrated by Webster and Casals to be entirely without antigenic properties. Apparently the newer ultraviolet treated vaccines have greater antigenic value. Some veterinarians have insisted that at least three doses be given in series to produce adequate immunization and this viewpoint seems justified.

There is however no test known to demonstrate that any given animal is actually immune. Immunization carries with it the danger of false security. Many people who have had their dogs vaccinated will therefore fail to co-operate in the continuation of the care that should be exercised until rabies has been completely eradicated. Only constant education of the public will emphasize the ever present danger of rabies even in a well cared for dog.

PREVENTIVE MEASURES FOLLOWING INJURY Following an injury by an animal certain procedures should be complied with. The word injury is used advisedly since bites are not the only important type of injury. Dogs, cats and other animals lick their paws and a rabid animal is most likely to be salivated which means that the claws may be contaminated with saliva. It is therefore unimportant whether a human injury has resulted from an animal bite or is the result of clawing by an animal.

The name, address and the age of the injured person, the site and the time of the injury and a description or identification of the offending animal should be immediately reported to the police or health department.

pound, completely isolated from all other animals. For legal reasons, it should be kept within the health jurisdiction in which the injury occurred. The animal should be carefully observed for a period of 14 days, if there is any sign of rabies this should be reported. The animal should be allowed to die from the disease, and the head should be carefully removed by a veterinarian, packed in ice and immediately transported to a reliable laboratory. A brain if not properly cared for, will deteriorate so markedly that a reliable examination for Negri bodies becomes impossible after a few hours.

In the laboratories of the Illinois State Health Department, it is customary to examine for Negri bodies at once and to do mouse inoculations on all cases where there is a question of human contact. This procedure verifies the microscopic diagnosis and, according to authoritative work it will pick up about 10 per cent more cases of rabies than can be found microscopically.

If the animal cannot be identified or apprehended, the injured person must be treated as though the animal had been rabid. In the case of injury about the head and neck, the antirabic treatment should be begun without delay. If the animal is not immediately found and the injury is about the trunk or extremities a 3 or 4 day delay is warranted until a concerted effort in locating the animal can be made.

Treatment of Wounds. The use of fuming nitric acid or phenol on wounds is still widely recommended, but the work of Shaughnessy and Zichis indicates that a 20 per cent solution of soft soap used to wash thoroughly and to irrigate wounds in animals is as effective as any type of chemical cauterization. A lacerated wound should not be closed by suture, in every case of primary suture, experience has taught that the reopening of the wound has been necessary because of infection.

The probability of acquiring rabies as the result of an injury from an offending rabid animal varies considerably according to the type and location of the wound. Babes of the Pasteur Institute has undoubtedly given the most authentic figures in his Table of Probabilities, he expresses in percentages the likelihood of developing rabies without treatment.

BABES' TABLE OF PROBABILITIES

Type and Location of Wound	Animal	Chance of Infection (Percentage)
Multiple deep—		
eyes, nose, lips	Wolf	100
eyes, nose, lips	Cats	70
eyes, nose, lips	Dog	60
rest of face	Dog	50
rest of bare areas	Dog	30
Single deep—		
fingers neck	Dog	15
Superficial—		
uncovered areas	Dog	10
if bled freely	Dog	2
Infected saliva		
on recent wound		01
on 24 hour old wound		00

A complete review of statistics on rabies is published in *The Tenth Report on Data of Antirabies Treatments*, compiled by Major Greenwood* and supplied by the Pasteur Institute. This includes the final summary of the health section of the League of Nations, and gives statistics on more than 1,250,000 series of treatments.

Of the 250,000 people treated during the period covered by this report, the overall mortality rate was 0.21 per cent lower than during any previous period. Of the 228,051 people treated there were 41 cases of postvaccinal paralyses with only 8 deaths. The total of 10 reviews of the League revealed that, of the 1,290,758 cases treated, there

accidents from the use of vaccine.

If these figures are compared with the percentage calculations in Babes' Table of Probabilities, it is obvious that the chance of any kind of postvaccinal paralysis is only one eighth as likely as the chance of acquiring rabies from contamination of a fresh wound by saliva. The chance of dying of a postvaccinal accident is only 1/4th as great as the chance of acquiring rabies from wound

* Bull. Health Organization League of Nations 11 12 301, 1945-46

contamination. It is difficult to reconcile these facts with the reticence some physicians show in the use of rabies vaccines. Physicians who do not hesitate to recommend a cholecystectomy in spite of known definite mortality may quiver at the thought of giving a series of rabies vaccine. This statement is not intended to encourage the useless administration of rabies vaccine but to give comfort to the physician who has to give such treatment. Hodges reports that the mortality is 30 times as high in untreated injuries from rabid animals as it is with vaccine treatment.

Rabies Vaccine. The Semple vaccine and the irradiated vaccine which is distributed by the Illinois State Health Department are the types of vaccine which are commonly used and have been proved safer than the older types. Following the work of Webster Casals and Habel, the antigenic properties of those now sold and distributed in this country are well established.

At the present time standard treatment consists of the subcutaneous injection of from 14 to 21 doses of one of the vaccines. The 21 dose treatment is most generally used for severe lacerated wounds from known rabid animals or for wounds about the head and neck. Two doses are to be given daily for the first week and one dose per day for the second week; these can be usually distributed over the outer sides of the arms and thighs. The anterior abdominal wall has been frequently recommended but modern clothing makes this location unsuitable. For wounds through clothing over the trunk and lower extremities 14 doses at one day intervals are usually administered.

Many physicians feel that fairly large doses of vitamin B complex given during the period of treatment may help to protect against paralytic accidents. This idea is not statistically supported at the present time but the use of this relatively harmless addition to treatment is recommended.

Several years ago Dr. Habel and again at the 1919 Convention of the American Medical Association Dr. Koprowski reported on the use of hyperimmune serum concentrates as the most promising development in years for the prophylactic treatment of rabies. Dr. Koprowski found that a single injection of hyperimmune serum around the area of the injury protected animals against

rabies more adequately than 14 doses of vaccine. The administration of the vaccine immediately following the use of the serum has not been as effective as delayed treatment. Dr. Habel feels that the serum should be given immediately after the injury then after a seven day waiting period, seven to 14 doses of vaccine should be administered for late effect. As the serum becomes available this should become the treatment of choice.

Even in the massive statistics of the League of Nations and the Pasteur Institute it is evident that a delay of 14 days from the time of the injury does not affect the mortality statistics in rabies and that an incubation period of less than 30 days does not allow for protection by rabies vaccine. Serum on the other hand has given immediate protection in a high percentage of cases and the reduction in number of necessary vaccine injections will reduce the number of post-vaccinal paralyses.

REACTION FROM RABIES VACCINE. The average patient who is given rabies vaccine will experience only mild discomfort; this has been the case where more than 200 series of vaccine have been administered. A reaction, which might be described as an Arthus phenomenon occurs in about half the cases. The patient experiences no discomfort during the first seven or eight injections but on the eighth or ninth day there will be a red, indurated itching area at the site of each previous injection which also appears subsequently at the site of each new injection. I have never found it necessary to discontinue treatment because of a reaction. I have seen only one case of multiple neuritis with considerable weakness followed by complete recovery of function. The literature contains many instances of encephalitis postvaccinal, paralysis transverse myelitis and some fatalities.

In recent years Dr. Sellers of Georgia has reported some fatalities. He and many others have emphasized particularly the danger of a repeated series of vaccine in patients who have been frequently exposed; they have concluded that fatal accidents do not follow any series of less than seven to 10 injections. It would seem rational that an individual who has been previously treated with a full series of vaccine will have a sufficient

stimulation of immunity following a booster series of seven doses. From the mortality rates, some physicians have concluded that one should never give vaccines to any person who has not actually been bitten by a rabid animal.

Cases of exposure without actual injury from the animal are unusual but they do occur. It is, therefore, recommended that a careful history and examination should precede any opinion as to the advisability of giving vaccine in each individual case.

INDICATIONS FOR USE OF RABIES VACCINE AND/OR SERUM. The necessity for giving rabies vaccine is the most serious decision to be made by the attending physician. This may be translated as follows: "Is the danger of the patient's contracting rabies from the injury in question greater than the slight risk incurred by the use of vaccine?" In spite of the recognized danger of such a procedure the generally accepted indications for the use of rabies vaccine and the special cases in which there might be some question in the minds of many physicians as to the advisability of giving vaccine are listed below.

Vaccine should be given if an individual has been injured

(1) by a wolf, fox, coyote, skunk or any wild animal that cannot be apprehended,

(2) by a rabid dog, cat, or other domestic animal,

(3) by a dog or cat that cannot be apprehended or identified

(4) by any of the above animals when the offending animal is deliberately killed less than 10 days after the injury,

(5) if an individual has been bitten by a healthy animal which becomes rabid within 14 days of the injury.

In any case where an animal dies or is killed, the brain should be examined microscopically and a mouse inoculation should be done. If the brain is in such a condition that these procedures cannot be carried out satisfactorily, one must assume that the animal was rabid. Opinions may differ in special cases, but experience and a thorough search of the literature would add the following indications:

(1) In the case of an animal injury about the head and neck, antirabic treatment should be given at once unless there has been no rabies within 50 miles during the

preceding year. The reason for this is naturally due to the short incubation period in such injuries, unless hyperimmune serum is available, rabies will not be prevented in the shortest of these periods, even by immediate treatment. Limited quantities of serum are available, as larger quantities become available, hyperimmune serum should be given at once and then discontinued for one week. If the dog is not rabid at that time, further treatment is unnecessary. If the dog has become rabid, a series of rabies vaccine should be given.

In one such case in which a 21 dose series was given, the patient became irritable, apprehensive, and feverish on the 10th day. His temperature reached 103° F by the 11th day and his muscles showed spasmodic twitching. The elder Dr. Lagorio, who was with the Pasteur Institute in Chicago, advised the continuation of the treatment. This was done and the patient returned to normal before the last dose was given. Dr. Lagorio felt that this represented an abortive case of rabies; he believed he had seen such cases twice previously. His impression was that the immunity was just sufficient to tip the balance in favor of the patient. My usual practice has been to give seven doses of rabies vaccine, beginning immediately following any head or neck injury. If the offending animal is well at the end of this time, treatment is discontinued and the results of observation are awaited.

(2) Antirabic treatment should be given to the patient who has been licked on mucous membrane surfaces by a rabid animal; this is particularly true of very young children or infants. Virus can penetrate the mucous membrane, at least one case of death from rabies is known in which the only established contact occurred when the rabid dog licked the vulva of the patient.

(3) Rabies vaccine should be given to any patient when there is grave suspicion or definite knowledge of contamination of a fresh wound with the saliva of a rabid animal. This indication requires careful history and examination. It is not necessary to give vaccine to everyone who has been in contact with a rabid animal, and vaccine should rarely be necessary for patients who have not been injured by a rabid animal. However, it should be kept in mind that there

have been cases of definite exposure in the absence of animal injury

TREATMENT OF RABIES After the onset of the disease rabies vaccine is entirely useless in the treatment of human rabies. All known cases, up to the present time have resulted fatally. The severe convulsive seizures are terrifying and painful. Anticonvulsant therapy, which may require large doses of intravenous barbiturates is indicated here the treatment would cease except for the possibility of help from recent developments.

One of these might be the use of large quantities of pooled human serum from patients who have been given rabies vaccine within a year. Evidence of effectiveness in other virus diseases is not good but if such serum should become available it might be worth trying. A procedure similar to that used in a severe case of tetanus by Dr. Vernon C. Turner and Dr. T. C. Galloway might be applicable here if we find that death in rabies may be due to secondary effects of the virus infection in the brain. Dr. Galloway has found to be the case in bulbar poliomyelitis. In the case of tetanus referred to curare was used as the anticonvulsant it was given to the point of respiratory paralysis. The patient was placed in postural drainage position—25 to 30° elevation of the feet—in a respirator and a tracheotomy was done to enable the maintenance of a clear airway. This patient recovered from tetanus. If such measures were used we might find that rabies is a self-limited disease and that by maintaining life through the acute stage the patient might recover from the infection.

Another promise looms large in the newer discoveries in antibiotics. Aureomycin and chloromycetin seem to be effective in diseases caused by certain of the larger viruses. Since the rabies virus is one of the largest with which we deal it would seem logical that animal trials should be begun at once to determine whether either of these antibiotics is effective in rabies.

MARTIN SEIFERT

REFERENCES

- Abercrombie T. F. Limitations of Antirabic Treatment. *J. M. A. Georgia* 35:132 1916.
- Archinbaugh W. E. Watch Your Dog! *Hygeia*, 13:233 1910.
- Bedson S. P. Virus Diseases Acquired from Animals. *Lancet* 2:571 1940.
- Bernkopf H. and Klugler I. J. Characteristics of Fixed Rabies Virus Cultivated on Developing Chick Embryos. *Proc. Soc. Exper. Biol. & Med.* 45:332 1940.
- Bernkopf H. and Nachtigal D. Complement Fixation Test with Sera of Animals Immunized with Rabies Virus. *Proc. Soc. Exper. Biol. & Med.* 53:38 1943.
- Boecker H. Tierversuche zur Frage der immunisatorischen Wirksamkeit von Wutschutzimpfstoffen aus formalisiertem Virus fixe. *Ztschr. f. Hyg. u. Infektionskr.* 121:735 1939.
- Bussell L. J. Myelitis after Antirabic Vaccine. Report of Fatal Case. *Lancet* 2:826 1946.
- Casals J. and Palacios M. Complement Fixation in Encephalitis and Rabies Virus Infections. *Science* 83:162 1941.
- Crowther W. M. L. H. Case of So-called Hydrophobia. Matter of Diagnosis. *M. J. Australia* 1:69 1946.
- Damon S. R. and Sellers T. F. Note on Probability of Error in Diagnosis of Rabies by Microscopic Search for Negri Bodies. *J. Lab. & Clin. Med.* 27:71 1941.
- D'Aunoy R. and Connell J. H. Report of Pasteur Institute of Charity Hospital of Louisiana at New Orleans for Year 1937. *New Orleans M. & S. J.* 90:648 1938.
- Denison G. A. and Dowling J. D. Rabies in Birmingham Alabama. Human Mortality Affected by Antirabies Treatments. *J. A. M. A.* 113:390 1939.
- Denison G. A. and Leach C. N. Incidence of Rabies in Dogs and Rats as Determined by Survey. *Am. J. Pub. Health* 30:267, 1940.
- Dunlap G. L. Comparative Value of Brains and Cords of Sheep in Rabies Vaccine. *J. Am. Vet. M. A.* 103:11 1943.
- Ellcott V. L. The Control of Rabies in the Metropolitan Area of Washington. *M. Ann. Dist. Columbia* 14:324 335 1945.
- Fife J. G. Case of Rabies in Man. *Lancet* 1:53 1943.
- Habel E. Personal Communication.
- Hampton B. C. Personal Communication.
- Hodes H. L., Webster L. T. and Lavin C. I. The Use of Ultraviolet Light in Preparing Non-virulent Antirabies Vaccine. *J. Exper. Med.* 72:437 1910.
- Hodges F. C. Unfavorable Reactions due to Antirabic Treatment. 3 Cases. *Am. J. Clin. Path.* 5:211 1935.

Webster, L. T., and Casals Arnet, J. Dog Test for Measuring Immunizing Potency of Anti Rabies Vaccines *J Exper Med*, 71 719, 1940
 Yen C H. Protective Value of Antiviral Serum in Experimental Rabies Infection *Proc Soc Exper Biol & Med*, 49 533, 1942

ACUTE POLIOMYELITIS

The treatment of poliomyelitis has been the subject of an abundant literature for at

least a century. The real contributions of each have been incorporated into our armamentarium and procedures of questionable value have been discarded. It is not the purpose of this section to deal with any particular regimen of therapy, but rather to present generally accepted methods of proved efficacy. This discussion will be limited to the acute course of the disease and hence will not deal with rehabilitation and orthopedic procedures.

Until recently the treatment of poliomyelitis was primarily the management and attempted correction of crippling sequelae. Our increasing fundamental understanding of the disease process has made it possible to recognize and emphasize the importance of the acute symptoms and findings. As a result, abortive and nonparalytic forms of the disease have been recognized with increasingly greater frequency. Further, we have

learned some of the baffling epidemiologic aspects of the disease. The latter group, having brain stem and cranial nerve nuclear lesions, is of paramount importance from the standpoint of mortality. Finally there is some evidence that an awareness and knowledge of early symptomatology leading to early diagnosis and proper expectant management may prevent the evolution of a classical paralytic illness.

The clinical diagnosis of poliomyelitis is a presumptive one and is usually made without difficulty. It is important, however, that we realize its presumptive nature. Spinal fluid and physical findings are frequently

absent in Guillain Barré syndrome, mumps, meningo-encephalitis, cerebrovascular accidents, and peripheral neuritis, must be constantly borne in mind. Further, we are forced to admit that there is no way of predicting which patient will experience a mild clinical course with eventual complete functional recovery, or, on the other hand, which individual will have extensive involvement with or without permanent physical handicap. In view of this circumstance it behooves us to maintain an attitude of intelligent skepticism in appraising the results for any particular form of therapy.

A direct approach to the treatment or prevention of acute poliomyelitis remains as a primary aim of the abundant investigational efforts now being concentrated on this disease. At present there is no antibiotic, chemotherapeutic, or biologic agent which

serum have not been substantiated. Our hopes for gamma globulin have been dissipated by such careful studies as that of Bahlke and Perkins. Although several theoretical possibilities for antiviral chemotherapy have been studied in experimental animals, only one, phenosulfazole (dirivisul), has seemed promising enough to warrant a trial in human subjects. It was found to be entirely ineffective (Grulee et al.). Although antibiotic substances such as sulfadiazine, penicillin, or aureomycin constitute important parts of the therapeutic management of bulbar, bulbospinal, and some spinal types of poliomyelitis, they are used only to control or prevent secondary bacterial infections and are not antiviral. It follows then that the treatment of poliomyelitis is indirect. Our efforts are directed toward counteracting the effects of the pathologic process by symptomatic therapy, physical means, and general supportive procedures.

Isolation Procedures. It has been stated that the occurrence of paralytic poliomyelitis is a coincidence in the process of mass exposure. Expressed in a different manner, at least during periods of high case incidence, the virus of poliomyelitis is so widespread that acquisition of the infection is more a function of individual susceptibility than of specific exposure. In the past, extreme isola-

tion precautions were practiced, based on ignorance and dread of the disease more than on specific knowledge of the manner of its spread. The presence of the virus has been demonstrated in the nasopharynx for periods of up to 8 days after the onset of symptoms (Howe et al.) The spread of virus from this source must be entertained as a possibility. Further, the presence of virus in the stools of convalescent patients for periods of 4 to 6 weeks is well established. Theoretically then it should be our purpose to protect against the possibility of respiratory spread during the first days of the clinical course and thereafter against enteric spread. In the former connection the use of face masks is far from ideal and, in fact, is

sterilization or feces is most difficult to accomplish by practical hospital methods. Finally, if proper sewage disposal is available the danger from fecal contamination is negligible. It is then recommended that dejecta be carefully handled and promptly disposed of into hopper or toilet without attempted sterilization.

Although health department regulations in some localities demand 3 weeks, 2 weeks is the most common requirement for isolation and recently a period of one week is being recommended as adequate. It is common practice to employ gown and mask technique with enteric precautions for 2 weeks though not attempting the sterilization of dejecta. The hands are carefully washed with soap and running water both before and after an isolated patient has been examined or, in the case of a poliomyelitis unit or ward upon entering and leaving the isolated area.

Prophylactic Measures. The physician is often called on to give advice concerning the avoidance of infection. As has been inferred previously, there are no specific biologic chemotherapeutic, or antibiotic substances available for this purpose. However, there are several general recommendations that can be made. In the majority of instances attempting to run away from poliomyelitis accomplishes little but to upset the normal pattern of living and thereby to increase the physical stresses to which children par-

ticularly are exposed. Further, the possibility of encountering the disease in the new environment is a real one. At times when poliomyelitis is epidemic, no illness however minor, should be neglected. The ailing individual should be put to bed and the advice of a physician solicited. All reasonable measures of personal hygiene should be emphasized in the home and elsewhere. Every effort should be made to maintain regular daily habits of living, avoiding physical, dietary and other excesses or indiscretions. It is reasonable to wash all uncooked foods and to boil drinking water for at least 5 minutes if there is a question of contaminated supply. In the latter connection it is pertinent to recall that no epidemic of poliomyelitis has been known to have been water borne. Finally the suggestion is frequently offered that unnecessary exposure to crowds should be avoided. This should not be construed, however, to mean that such regulated public gatherings as schools and theaters should be categorically advised against. Actually the relative risk of school exposure is probably much less than that incurred during the uncontrolled play activities of children. On the other hand, the opening of a rural school during a local epidemic of poliomyelitis could afford a common exposure of geographically isolated individuals in which case it should remain closed temporarily. The question of whether public and semi-private swimming pools should continue to function during epidemics is a difficult one. If superchlorination of the water is accomplished and further if excessive fatigue and chilling are not incident to use of the pool its continued operation is acceptable though not necessarily desirable.

Psychologic Considerations. The impact of acute poliomyelitis upon patients, their families and communities can be devastating. In considerable part this unfortunate reaction can be prevented. In the first place physicians must assume responsibility in fostering public education concerning the disease. In addition, they must help to outline a positive program for their community and to denounce firmly the imposition of ridiculous and unjustifiable measures stemming from and in themselves contributing to public hysteria. A few minutes spent describing the disease, explaining the condition of the

patient and answering the questions posed

ner The family can be cautioned against the overt display of their apprehension in the patient's presence and as a consequence of these changes in familial attitude most effective reassurance can be furnished the patient Among professional personnel an attitude of confidence friendliness and businesslike but unfrenzied performance of all necessary procedures cannot be overemphasized Finally by the intelligent use of diversional therapy such as reading music games and other forms of simple entertainment depressing introspection and loneliness can be minimized

Fluids and Diet The usual acute clinical course of poliomyelitis does not exceed 7 to 9 days Unless there is respiratory dysfunction

adequate to furnish the optimal daily requirements are desirable as in any well conceived dietary Certainly vitamin or caloric deprivation is not justified as a therapeutic measure with the possible exception of the patient remaining relatively immobilized for long periods by reason of quadriplegic involvement or need of artificial respiration In these cases moderate restriction of milk and the withholding of supplementary vitamin D are justified because of the danger of renal calculus formation

Parenteral alimentation is resorted to when danger of respiratory obstruction exists as is the case when diaphragmatic or intercostal musculature is paralyzed and lesions of the glossopharyngeal or vagus nuclei result in swallowing difficulty or again in the bulbar patient when damage to the cardiorespiratory centers in the dorsal reticular formation of the medulla gives rise to irregular shallow respirations with variable periods of apnea If the patient requires artificial respiration and is enclosed in a cabinet type of respirator intravenous subcutaneous or rectally administered fluids can nevertheless be given without appreciable difficulty by utilizing the small stoppered port in the roof of the respirator A fitted cork penetrated by a short

section of sterile glass tubing is attached to the infusion equipment In general terms the quantity of fluid administered varies from approximately 50 cc per kilogram of body weight per day in the adult to 125 cc per kilogram per day in very young children Of this total calculated amount not more than one third is allowed to be salt-containing Obviously under circumstances of excessive sweating or repeated vomiting such a rough rule as the above does not apply and one must be guided by careful clinical appraisal and the determination of blood electrolytes Five per cent glucose in sterile distilled water which is isotonic with the blood plasma serves adequately to make up the remainder of the daily fluid requirement In those instances in which technical difficulties preclude the possibility of the intravenous administration of fluid hypodermoclysis and proctoclysis can be utilized to great advantage

Before leaving the subject of parenteral fluid administration mention should be made of the use for specific therapeutic purposes of two intravenous solutions namely hypertonic glucose and hypertonic saline with repeated lumbar drainage of cerebrospinal fluid The hypothesis that hypertonic glucose solutions favorably affect the inflammatory process within the central nervous system is supported only by the clinical impressions of a few observers The second therapeutic approach listed above has been generally abandoned as ineffective and as not without

Gavage feedings constitute a most useful and convenient method of providing nutrition to selected patients with impairment of pharyngeal or respiratory function However in either type of case it must be initiated with the greatest care and only after progression of the clinical findings has ceased for at least 24 hours If this precaution is not observed there is great risk of crucial difficulty with excessive mucus stimulated by the introduction of the tube Such an occurrence in a critically ill patient with the resultant hypoxic episode can be and not infrequently is fatal A thorough trial of 5 per cent glucose or normal saline precedes the administration of milk amino acid prep-

irations or high caloric fluids by this route. In our experience the use of a polyethylene tube approximately $\frac{1}{16}$ in diameter is ideal for gavage purposes. Through it a constant drip can be maintained with the rate of flow so adjusted as to prevent overfilling of the stomach. Any one of several high caloric feedings of known composition is suitable.

Elimination. Constipation is an early and common complaint in acute poliomyelitis and may persist for as long as 2½ weeks. In the majority of instances this difficulty is thought to be due to temporary derangement of the motor innervation of the bowel but of course there are also patients in whom paralysis of abdominal and diaphragmatic musculature is a contributing factor. Frequently a warm saline enema every second or third day is all that is required. Mineral oil by mouth or occasionally as a small retention enema at night is helpful and rarely is the digital disruption of a fecal impaction required. Strong cathartics and saline purges should be avoided. Fortunately the patient may be assured of complete return of proper bowel function.

Urinary dysfunction during the acute course of this disease is considerably less frequent than constipation but may be quite severe, disturbing to the patient and trouble some to manage. All degrees of urinary dysfunction may be encountered from slight difficulty in initiating micturition to complete retention. Since the duration of even severe manifestations is rarely more than a few days, serious complicating infection can usually be avoided by intelligent management. The presence of urinary dysfunction in small children and infants may be missed since attendants interpret overflow dribbling as the normally frequent urination of this age group. The simple expedient of inspecting the lower abdomen for fullness in the midline and palpation with percussion of vesical dullness will reveal the true state of affairs. The trial of such maneuvers as attempted micturition in the sitting position, pouring warm water over the perineum and hot sitz baths are helpful in mild cases and should be tried. Occasionally a patient will be able to void if allowed to recline in a bath tub of warm water. A next logical step is the use of parasympathomimetic drugs. The most useful of these described by Law

son and Garvey in 1947 is furfuryl trimethyl ammonium iodide or furmethide. It is given orally in doses varying from 1.25 to 7.5 mg. Unfortunate side reactions are not frequent and since the drug is rapidly dissipated the dosage may be repeated after 30 to 45 minutes. In a small percentage of patients catheterization must be resorted to. Since the expected duration of urinary dysfunction is short the bladder is emptied on one or two occasions by simple catheterizations before

gram for a child or 3 to 5 gm per day for an adult. Rarely is an indwelling catheter essential. In addition to the danger of detrusor paralysis in the male, some authors state that urinary dysfunction is prolonged if this expedient is resorted to (Horstmann).

Physiotherapy. In a disease which is associated with paralytic manifestations as well as variable degrees of tightness or spasm of the muscles of the body, a respect for body mechanics and the intelligent application of

second the prevention of early deformities and the overstretching of muscles, third the promotion of optimal nutrition of muscle tissue which has temporarily at least been deprived of normal innervation. Finally but not of least importance is the use of positioning as a part of general therapy for the patient. Reference is made here particularly to the dependent drainage of secretions from the oropharynx and tracheobronchial tree in the prevention of both respiratory obstruction and hypostatic pneumonia.

All gradients of postural drainage can be employed from elevation of the foot of the bed on 10 to 12 inch blocks to short intervals of completely inverted position with the head and trunk dependent over the side of the bed. Also in extensively paralyzed and respirator patients frequent changes in position are required to minimize the danger of pulmonary infection and to prevent the development of decubiti.

Routinely the standard type of hospital bed is prepared by placing boards between the spring and a firm mattress. A vertical

footboard blocked away from the foot of the mattress, a distance of approximately 4 in., serves the double purpose of providing a flat surface against which the feet can be maintained at a 90° angle to the long axis

greatly to comfort. Small pads under the knees and the small of the back in the supine position and under the dorsum of the foot and anterior aspect of each shoulder when the patient is prone can be justifiably used early in the clinical course if these relieve discomfort. Towel rolls or sandbags are used to prevent lateral rotation of the legs. The upper extremities are placed at the sides or are slightly abducted with the elbow joint extended. It should be remembered that variations from these standard positions are frequently necessary in individual circumstances.

Green has divided the clinical course of poliomyelitis into the acute febrile stage, the sensitive period of convalescence beginning approximately 48 hours after the return of the body temperature to normal, the insensitive period of convalescence which may last as long as 16 months, and finally the chronic stage. We are here concerned with the first two subdivisions of this classification. The application of physiotherapy in the febrile stage is limited to relief of discomfort. Subsequently in the sensitive period of early convalescence efforts toward the control of pain are continued, but in addition particular attention is directed toward the prevention of deformities and toward the promotion of optimal conditioning of all muscles in expectation of restored innervation and the disappearance of tightness.

In accomplishing the first of these ends, namely, the relief of pain, heat is still the most effective form of therapy. Green has shown that moist heat applied to the skin is capable of increasing the temperature of underlying musculature as much as 6 to 10° F. In addition to relieving the subjective discomfort, there is a marked increase in the volume of circulation to the part. Equally interesting is the further observation that this elevation of muscle temperature continues for 2 to 3 hours after the pack is removed, provided the extremity is covered by

the bedclothes. Moist heat can be provided by the Kenny type of wrap-around pack which is cut to fit the skeletal part to be treated, or by so-called lay-on packs, and also by hot baths. The choice of the particular form of heat to be used can then depend on individual treatment situations. Wrap-around packs have the disadvantage of being costly and difficult to apply properly. Lay-on or prone packs need not be specifically cut to fit individual patients and are easily applied by a single person. The patient is placed in a face down position in preparation for the procedure. One large pack, carefully tucked around the sides of the body, is used for the neck, trunk and buttocks, while similar rectangular packs are applied to the entire extent of each lower extremity. The same materials are used in each type of pack. Two layers of woolen blanketing are taken from boiling water and carefully wrung out. These are applied to the part as hot as the patient will tolerate, care being taken to avoid wrinkles and are covered with a waterproof material such as koroseal. An outer layer of insulation, usually dry flannel, is finally applied. There is now general agreement that packs three or four times daily for 30 minute periods are the maximum necessary (Green and Gucker), and that a sleeping patient

applying moist heat, but are not generally practiced until convalescence has been well established. Further, personnel and equipment for transporting the patient must be available. A Hubbard tank is ideal for this form of hydrotherapy, but a large bath tub also will serve the purpose. Luminous heat is recommended by some (Hayne), but is not as effective as moist heat and is not widely used.

Other physiotherapeutic procedures, notably passive exercises, are not undertaken until after the temperature has returned to

daily Active exercises and muscle stretching are delayed until the asensitive phase of convalescence has been reached

Medication The advisability of routinely

to mind If penicillin is chosen it is logical to choose a long acting preparation in order to reduce to a minimum the number of necessary injections The possibility of orally administered aureomycin ultimately becoming the drug of choice seems likely

The question of sedation is among the most pressing and difficult problems in caring for seriously ill patients Extreme caution should be the keynote of our thinking in this connection There is now abundant evidence of widespread damage to the central nervous system in poliomyelitis Damage to medullary centers has been demonstrated at necropsy in patients who had shown no clinical signs of such localization The imposition of further depression on already damaged centers may be crucial Restlessness and irrationality can be erroneously interpreted as indications for sedation In the presence of these findings almost universally the need for oxygen not sedatives Certainly every attempt at improving aeration and oxygenation of the blood should be made before sedatives are given This will be discussed further in connection with hypoxia Occasionally severe headache or pain in tight muscles incompletely relieved by heat interferes sufficiently with rest as to demand attention Not infrequently 10 to 15 grains (0.6 to 1.0 gm) of acetylsalicylic acid will control symptoms to the point where rest is possible Barbiturates such as phenobarbital and secobarbital in doses of $\frac{1}{2}$ to $1\frac{1}{2}$ grams (32 to 100 mg) may be necessary and can be given with relative safety in most instances Rarely small doses of demerol may be justifiable as suggested by Horstmann Morphine and codeine should not be used

Attempts at the control of spasm by the use of drugs has not been particularly successful Derivatives of curare have been strongly advocated by some (Ransohoff) but must be given with extreme care since the margin between the dosage producing adequate relaxation and that causing paralysis is narrow If excessive doses are given arti-

ficial respiration is frequently required Because of the associated dangers plus the fact that considerable doubt as to the usefulness of the drug is reported (Richards et al) it is not recommended for general use In 1943 Kabat and Knapp introduced the use

subcutaneously is recommended Although reported results vary considerably there is a general agreement that moist heat is more efficacious and to be preferred At least it can be said that further studies of prostigmine are necessary before its general acceptance can be advised A final approach to the problem of directly and quickly relieving spasm has been through the production of a paravertebral sympathetic block (Collins et al) Here too only further experience can disclose the efficacy of this procedure in the treatment of poliomyelitis

The use of one additional type of medication should be mentioned before concluding this portion of the discussion The reduction of excessive secretions would seem to be desirable in patients having difficulty in swallowing as a result of lesions in the cranial nerve nuclei Atropine or ephedrine has been used occasionally for this purpose in the past The practice is mentioned only to condemn it In actuality the net result of atropine administration in this circumstance is the increased viscosity of previously more fluid secretions without important reduction in their quantity As a consequence the patient who is already having trouble clearing his airway of secretions experiences greatly increased difficulty

Respiratory Obstruction and Failure Mortality rates in poliomyelitis as reported from various epidemics range from 5 to 25 per cent Almost without exception in fatal cases cervical spinal cord lesions resulting in paralysis of the principal muscles of respiration and/or lesions in the cranial nerve nuclei and respiratory center of the medulla giving rise to airway obstruction or respiratory failure are present In order to discuss therapy in this group properly let us first consider briefly the causes of their common difficulty namely inadequate oxygenation of the blood or hypoxia Elam has suggested that the respiratory difficulties in poliomyelitis can be

divided into two general categories. Ventilatory deficiency is the first of these and refers to faulty transport of gases between the lungs and surrounding atmosphere. It is found when there is paralysis of the intercostal muscles or diaphragm when the respiratory center is depressed, and when obstruction of the upper airway is present. The second category is alveolar deficiency or insufficient transfer of oxygen from the alveoli into the blood. Pulmonary edema, atelectasis and pneumonia all produce this effect. Not infrequently components of both ventilatory and alveolar deficiency are present concurrently in the same patient.

Four general means of clinical management are available in combating improper oxygenation from these causes. They can be listed as follows:

- (1) Artificial respiration
- (2) Suction of secretions from the airway
- (3) Tracheotomy
- (4) Oxygen administration

It is quite apparent that an individual exhibiting paralysis of the muscles of respiration needs only the mechanical support to respiration supplied by a respirator. If however, respiratory failure is the result of central depression, it has been stated that the respirator is of little value. Our own experience, supported by spirometric studies (Grulee et al.) however, does not lead to the same conclusion. The usual objection

to the contrary, in the presence of central respiratory failure, mechanically induced respiration should be employed if the minute respiratory volume is inadequate and if oxygen alone does not correct clinical evidences of hypoxia. If the patient in question also gives evidence of innervational defects of the hypopharynx, the need for artificial respiration remains unchanged but before it can be instituted tracheotomy is usually mandatory. The indications for this procedure will be discussed later.

Too little definitive information is available concerning respirator management. Although the suggested ranges for pressure and rates of cycling the mechanism are given

at 0 to 20 cm. of water negative pressure, and 18 to 24 respirations per minute (Wilson), adjustments for individual patients within these limits have been reached empirically. Drinker, who perfected the first

equally true at the present time, as Elam has pointed out. The axiom of adjusting the respirator to the comfort of the patient must be supplanted by more exact standards since settings which result in hyperventilation are usually chosen by the patient. If continued,

interpreted incorrectly as evidence of insufficient ventilation. Further after the body has adjusted to a lowered carbon dioxide tension any decrease in ventilation gives rise to subjective symptoms. These in turn may be attributed to inadequate ventilation and lead to a completely erroneous adjustment of the respirator. The periodic determination of the carbon dioxide combining power, pH, serum protein and chloride content of the

method of following respirator patients is the determination of minute volumes of respiration by using a standard BMR machine (Grulee et al.). The mouthpiece is replaced by an oronasal mask and the reservoir filled with oxygen or air (usually the former). The inspiratory tidal volume is determined by measuring the upward deflection of the writing point with each respiration. These are totaled for a one minute period to obtain the minute volume of respiration. The technique can be repeated as often as desired whether the respirator is operating or not, and in most situations gives an objective criterion for judging pulmonary ventilation. If however, alveolar deficiency is present the minute volume of respiration will not reflect the faulty transport of oxygen from the alveoli to the blood stream. Determinations of arterial

in the near future to supplant more time-

consuming and troublesome chemical analysis

Obstruction of the upper airway can be produced in one of three ways. The most common is the pooling of secretions in the hypopharynx as a result of the inability of the patient to swallow or cough. The second mechanism is closely related to the first since the presence of pooled secretions may lead to reflex closure of the glottis. Finally, upper airway obstruction infrequently is produced by the apposition of the vocal cords in the midline as a result of partial though not complete paralysis, or spasm of their associated musculature.

The mechanical removal of secretions requires continual alertness by a trained observer, and is greatly aided by proper postural drainage. A constant source of mechanical suction such as is offered by any one of several commercially available units is satisfactory. The negative pressure should be set at 5 to 7 lbs. per square inch and a catheter used as a suction tip. The latter should be provided with several openings in the distal 1/4 in. of its extent, and the end should be carefully inspected for sharp edges. Mechanical abrasion of mucous membranes by the tip of the catheter as well as by ap-

every effort is made to avoid its prolonged use at any one time. This is of especial importance when aspiration is being accomplished through a tracheotomy cannula, in which case a maximum of 2 minutes should not be exceeded. In convalescent bulbar patients it is often expedient and probably desirable for the patient to carry on necessary aspiration himself. In this circumstance, a curved metal tip, as is used in anesthesia, may be preferred.

Not infrequently suction of the oropharynx, however conscientiously applied, is incapable of preventing aspiration of secretions by the

. . .

realized, however, close teamwork with an experienced laryngologist minimizes this hazard. The decision as to when aspiration

of secretions through the natural airway should be abandoned in favor of the more radical procedure of effecting tracheotomy or introducing an endotracheal tube cannot be arbitrarily reached on the basis of one or two clear cut signs. Rather, all aspects of the immediate clinical picture and reasonable predictions for the immediate future are carefully considered. Certainly tracheotomy should be performed as early as possible if its need can be anticipated. By the same token, the mere presence of clinically demonstrable lesions of the glossopharyngeal and vagus nerves is not an indication since a majority of these will recover without surgery (Grulee and Panos). If however, an individual is experiencing a fulminant illness of short duration with steadily increasing evidences of bulbar damage, tracheotomy should be performed in anticipation of imminent central respiratory failure* and the consequent need for artificial respiration. Similarly, if definite pooling of secretions and loss of the ability to cough are complicated by the appearance of paralysis of the muscles of respiration of such severity that the support of a respirator is, or soon will be required, the operation must be performed. If it is not, the action of the machine will necessarily lead to massive aspiration. Finally, patients in whom moderately severe obstruction to the airway exists will show retraction of the intercostal spaces. In the presence of this sign, even though an apparent cause of obstruction is not found, tracheotomy should be seriously considered.

In the preceding paragraph some of the indications for tracheotomy based on the presenting neurologic manifestations and objective mechanical phenomena are described. Since the effect of these lesions is the production of hypoxia, it is pertinent that we direct our attention to the clinical signs of this condition. One of the earliest and most helpful is an increase in the pulse rate. Sometime later a moderate increase in arterial blood pressure can also be expected. Irrationality and extreme restlessness are evidence that hypoxia of moderate degree is present, probably combined with some carbon dioxide accumulation. Next in the sequence of increas-

* The respiratory center is anatomically adjacent to the nuclei of the 9th and 10th cranial nerves.

ing severity ■ the appearance of drowsiness. Finally cyanosis and coma supervene. The continued presence or progression of signs and symptoms of hypoxia not responding to oxygen therapy, artificial respiration, or at tempted removal of obstructions to the airway suggests the need of tracheotomy.

Endotracheal intubation is infrequently employed as an alternative to tracheotomy. However, the danger of damage to the vocal cords ■ great, the tube ■ disturbing and uncomfortable to the patient, it cannot be allowed to remain in place for more than a few hours, and, finally, it accomplishes no more than a tracheotomy does. For entirely similar reasons, the insertion of "lifesaver" tubes through the larynx has been abandoned.

The final tool with which we can combat respiratory failure and the effects of airway obstruction is oxygen therapy. True contraindications to its use are from a practical standpoint, nonexistent. The possibility of oxygen toxicity is real only if 100 per cent oxygen is breathed over long periods of time and concentrations of this magnitude are most difficult, if not impossible, to attain under the usual conditions of administration.

Under special conditions or high grade obstruction to the airway it is desirable to employ helium with oxygen since the great diffusability of the former aids in the delivery of oxygen beyond points of obstruction.

If oxygen fails to produce desired results when the indications for its use seem clearly established, technical factors are almost invariably responsible. The importance of checking cylinder pressures, regulator performance, flow rate meters, humidification bottles, and oxygen lines to tent, mask, or

other techniques. These tests should sample gas from the immediate vicinity of the patient's face, since the oxygen being introduced may be displaced upward by heavier carbon dioxide which, in turn, is actually smothering the patient. With some types of equipment then, flow rates must be adequate to flush out accumulated carbon di-

oxide or oxygen therapy ■ not beneficial. This case is cited as an example only, and does not constitute a basic criticism of the use of tents in therapy.

The administration of oxygen by nasal catheter has many advantages: a minimum of elaborate equipment ■ necessary, the patient is more easily cared for as regards feeding, aspiration of secretions, etc., and, most important, the oxygen concentration obtainable through a properly placed nasal catheter ■ adequate in ■ majority of therapeutic situations. The technical details of the procedure are simple but important. In the first place, ■ soft 12F to 14F catheter is selected and several small apertures are made near its tip. Before insertion the distance from the tip of the nose to the tragus of the ear is measured on the catheter. The tube is then introduced to this depth or until gagging or gulping occurs. It ■ then withdrawn approximately 1 cm and fastened securely in place. Flow rates of 4 to 6 liters per minute using this method can be expected to yield up to 60 per cent available oxygen concentrations. If the patient in question has been subjected to tracheotomy, the catheter may be introduced into the inner cannula. In the presence of pulmonary edema the intermittent introduction of oxygen under 2 to 4 cm of water pressure is highly desirable (Grulee and Elam). Although this is usually accomplished through the tracheotomy cannula, oxygen must also be given by an oronasal mask to prevent dissipation of the positive pressure upward through the oropharynx. The reader ■ referred to source material for the technical details of the procedure.

Oxygen by mask ■ of limited usefulness, in large part because of poor acceptance by the patient. In the absence of palsies of the ninth and tenth cranial nerves, however, an oronasal mask is entirely acceptable for oxygen therapy. The interesting possibility of

too remote and could furnish an efficient alternative to the conventional respirator.

In conclusion, it can be said that oxygen

liberally, since, to be of greatest value it should anticipate, not follow, the appearance of severe hypoxia

CLIFFORD G GRULEE, JR

REFERENCES

- Bahlke A M and Perkins J E Treatment of Preparalytic Poliomyelitis with Gamma Globulin *JAMA* 129 1146 1945
- Collins V J Foster W L and West W J Vasomotor Disturbances in Poliomyelitis with Special Reference to Treatment with Paravertebral Sympathetic Block *New England J Med* 236 694 1947
- Green W T Present day Status of Poliomyelitis *New England J Med* 238 73 1948
- Green W T and Gucker T Moist Heat in the Treatment of Poliomyelitis *Am J Med* 11 606 1949
- Grulee C G and Elam J O Round Table Discussion Poliomyelitis *Pediatrics* 1 634 1948
- Grulee C G and Panos T C Epidemic Poliomyelitis in Children Clinical Study with Special Reference to Symptoms and Management of Bulbar Polioencephalitis *Am J Dis Child* 75 24 1948
- Grulee C G Eldridge F L and Ford G M The Clinical Study of Pheno Sulfazole in Acute Poliomyelitis (To be published)
- Grulee C G Eldridge F L and Ford G D The Use of Spirometry in the Practical Management of Patients in Respirators (To be published)
- Hayne A Personal Communication
- Horstmann D M Clinical Aspects of Acute Poliomyelitis *Am J Med* 6 592 1949
- Howe H A Bodian D and Wenner M A Further Observations on Presence of Poliomyelitis Virus in Human Oro-pharynx *Bull Johns Hopkins Hosp* 76 19 1945
- Kabat H and Knapp M E Use of Prostigmine in Treatment of Poliomyelitis *JAMA* 122 939 1943
- Lawson R B and Carvey F A Paralysis of Bladder in Poliomyelitis *JAMA* 129 1146 1945
- Ranschoff N S Curare in Acute Stage of Poliomyelitis *JAMA* 129 129 1945
- Richards H L Elkins E C and Corbin M B Curare in Treatment of Poliomyelitis *JAMA* 122 939 1943
- Wilson J L *The Use of the Respirator in Poliomyelitis* New York National Foundation for Infantile Paralysis Publication No 23 1947

DENGUE FEVER

The treatment of dengue is entirely symptomatic. Bed rest and sponging are required during the febrile periods. Aspirin 0.6 gm should be given freely to help relieve the severe headaches and bone pains. Codeine

in small doses, 30 mg, is useful, especially at night. When prolonged vomiting occurs morphine sulfate, 15 mg by hypodermic injection should be given. Convalescence is marked by prolonged muscular and nervous asthenia. A change from the hot humid tropics to a more temperate climate is helpful during this period. Extended rest and preparation for freedom

Prevention requires control of the mosquito vector (Zeligs et al). Because the common vector is *Aedes aegypti*, a "domesticated" mosquito, the strictest attention must be given to breeding places in and around houses. Eradication of the species should be the goal. Personal protection by the use of nets and repellants is effective in the individual case, but these measures cannot be relied on to protect a population.

Immunity following an attack is of brief duration; hence epidemic dengue may recur in an area at intervals of a few years. Dependable vaccines have not been developed.

HENRY R JACOBS

REFERENCES

- Carson D A Observations on Dengue *U S Nav M Bull* 42 1081 1944
- Ewing D Q Dengue Fevers *M Clin North America* 28 1471 1944
- Kaplan A and Lindgren A Neurologic Complications Following Dengue *U S Nav M Bull* 45 506 1945
- Webster H Dengue Fever *M Clin North America* 31 1267, 1947
- Wilbur C L Jr Control of Dengue in Hawaii *Am J Pub Health* 37 663 1947
- Zeligs M A Legant O and Webster E H Epidemic Dengue Its Abortion in Combat Area *U S Nav M Bull* 42 856 1944
- Zussman H M Dengue Fever in Australia Brief Review of 1000 Cases Treated *M Rec* 157 007 1944

YELLOW FEVER

This illness has two phases: an early invasive period lasting from 2 to 5 days during which the virus multiplies enormously, and a later period of intoxication due to release of products from damaged and dead cells of the liver and other organs. There is perhaps no disease that deals with parenchymatous

cells so savagely and treatment can only preserve what is left.

There is no specific treatment of yellow fever. Immune serum although quite effective in experimental animals when given with the virus has little use in a clinically recognizable case. Immune serum has therefore not been made available. No chemotherapeutic agent has a demonstrable effect nor is penicillin of value. Streptomycin has not been reported on nor has aureomycin or chloromycetin. (Perhaps newer antibiotics may appear which will be virucidal or perhaps it will be possible to alter the intracellular medium in such a way that multiplication of virus is hampered.)

Supportive treatment is all that can be given to the patient. If he is seen early in the disease he may be moved a short distance to a place where he will have absolute bed rest and better care but if he has been ill for 2 days or more he must not be disturbed. On the first day of illness a saline purge may be risked thereafter only enemas should be employed as the need arises. The severe epigastric pain and the excruciating headaches may be treated with codeine 30 mg. or morphine 15 mg. by mouth if vomiting has not begun by hypodermic if it has. Incessant vomiting is hard to relieve. Cracked ice and cocaine hydrochloride $\frac{1}{4}$ grain (15 mg.) by mouth and ice caps to the head and to the epigastrium may be tried. The loss of blood through vomiting and by diarrhea is usually not significant but careful attention should be given to dehydration. Parenteral liquids only should supply the need. Large volumes rapidly administered must be avoided.

Some thought has been given to measures which might help to preserve the cells of the liver. Sellards and McCann believed that choline hydrochloride exerted a beneficial effect on the liver in experimental yellow fever in monkeys. Possibly methionine will be found to behave similarly although it is hard to believe that measures of this sort will prove significant. The use of amino acid solutions intravenously is not advisable.

Conservative treatment throughout is imperative. Men with a large experience (Soper) dwell on this note and until some valuable and specific measure is found the patient will fare better if he is not subjected to random overtreatment. Antipyretics and

other drugs should be used sparingly. Conservatism must extend well through convalescence even though recovery in nonfatal cases is amazingly rapid. The patient must follow a mild regimen for several weeks after the fever has subsided.

Prophylactic treatment consists in immunization. Vaccination with yellow fever vaccine confers solid immunity on a high percentage of persons. The administration of the vaccine is better left to organizations skilled in the practice. Persons to be immunized should be sent to the medical departments of the Army or Navy, to the National Institute of Health, or to the Rockefeller Institute. The use of the vaccine is described in a "Form Letter" by the Surgeon General.

HENRY R. JACOBS

REFERENCES

- Directions for Use of Yellow Fever Vaccine in Immunization against Yellow Fever. War Med. 149 1941.
 Sellards A. W. and McCann W. S. Choline hydrochloride in Experimental Yellow Fever in Rhesus Monkeys. U. S. War Med. Bull., 43 120 1941.
 Soper F. L. Treatment of Yellow Fever. J. A. M. A. 118 374 1942.

PHLEBOTOMUS FEVER

(Sandfly Fever, Pappataci Fever, Thee Day Fever)

Treatment of phlebotomus fever is entirely symptomatic. The disease has no mortality and complications are rare. Relief of the severe pains and aches is afforded by generous use of aspirin (0.6 gm.) or of the aspirin-phenacetin-caffeine compounds with an evening dose of 30 mg. of codeine. In rare instances the agonizing headache may be helped by lumbar puncture although this measure must be reserved for the exceptional case.

Prophylaxis depends entirely on avoiding the vector of the disease, the sandfly *Phlebotomus papatasi* which bites at night. Fine meshed bed nets and the use of di-methyl phthalate as a skin repellent are useful measures. Attempts to create a vaccine seem to have led only to indefinite results thus far. A first attack confers immunity for approximately a year but subsequent attacks are milder.

HENRY R. JACOBS

FOOT AND MOUTH DISEASE

(Aphthous Fever)

Foot and mouth disease in man appears only during prevalence of the disease in cattle or other domestic animals. The disease is rarely fatal, and then usually only because of special circumstances. The vesicular eruption on the mucous membranes of the mouth causes pain and salivation, alkaline and antiseptic mouthwashes may be employed freely to relieve the patient. Cauterization of the aphthae with solid silver nitrate is helpful. The symptoms of burning, paresthesia, and pain in affected areas may be alleviated by 10 grains (0.6 gm.) of aspirin or 30 mg. of codeine and by the application of anesthetic ointments. Because the disease is highly contagious, the proper precautions must be observed.

HENRY R. JACOBS

LYMPHOGRANULOMA VENEREUM

The patient should be put at rest and sulfathiazole given in 1 gm. doses every 4 hours. Careful attention should be paid to blood levels and the blood count and urinary findings. An optimal blood level of 6 to 10 mg. per cent is desirable.

The Frei antigen is used in treatment. Gradually increasing doses are given beginning with 0.2 cc. every other day for eight doses. Roentgen therapy has been used in markedly chronic infections. Late chronic lesions, such as elephantiasis due to lymph edema caused by lymph blockade, may require surgical treatment. Not infrequently anal stricture may develop and require rectal surgery, together with medical treatment. Penicillin is of no avail in treatment, nor has any success been reported with streptomycin.

Recently aureomycin has been reported to be beneficial in this disease, in a dose of 10 to 40 mg. per day, administered intramuscularly. Treatment is usually continued for one week. The effect of aureomycin is most marked in the acute case, and it is possible that larger doses may be indicated to pre-

In the chronic cases, 500 mg. of aureomycin every 6 hours is a valuable adjunct surgical drainage of the lesions.

JAMES I. FARRELL

ACUTE GASTRO ENTERITIS

Acute gastro enteritis is a symptom complex which may be due to a variety of etiologic factors. Bacterial or virus infection, bacterial toxins or putrefaction products in food and food idiosyncracies are thought to account for the majority of cases. Only symptomatic measures can be employed in treatment since the exact cause cannot, as a rule, be determined. Although it is usually unnecessary to make an exact etiologic diagnosis, in certain instances, such as acute amebiasis and acute arsenic or mercury poisoning it is essential for proper treatment. In all persistent cases or where there is failure of response to treatment a careful search for the causative factor must be instituted.

Nausea and vomiting and diarrhea with intestinal cramps are the primary symptoms and may each be present in various degrees. In mild cases the nausea, vomiting and cramps may be controlled with 10 minims of tr. of belladonna given four times daily with 0.4 mg. of atropine sulfate subcutaneously. Paregoric, 4 cc. three or four times daily, is also effective. For the diarrhea, bismuth subcarbonate, kaolin, or kaolin pectin mixtures are satisfactory. Fluids and food should be strictly limited for 12 to 18 hours. A light diet may then be allowed for the next day or two. Treatment with castor oil or other laxatives is mentioned only to be condemned.

In severer cases it is necessary to employ more strenuous measures. Water and salt loss should be controlled as promptly as possible since in our experience this is the most effective means of shortening the duration of disability as well as providing symptomatic relief. Deodorized tincture of opium, 1 minims as an initial dose and 5 minims every 3 hours as necessary, is most satisfactory for this purpose. Occasionally hypodermic medication is necessary. In this case 15 mg. of morphine and 0.4 mg. of atropine can be used. When vomiting or diarrhea has been excessive or is persistent 1000 cc. of 5 per

cent glucose in normal saline should be administered by vein

The patient should be kept in bed for 24 hours. As soon as the nausea has subsided small amounts of fluid and soft light foods may be offered. Sufficient medication should be given for several days to prevent a recurrence of symptoms. During convalescence diarrhea may be controlled as in the milder cases.

RICHARD B. CAPPS

ACUTE INFECTIOUS HEPATITIS AND HOMOLOGOUS SERUM HEPATITIS

Prophylaxis. Acute infectious hepatitis is contagious through the fecal-oral route and consequently appropriate isolation measures are indicated. Only scant data are available regarding the persistence of the virus in the feces but in most cases 4 weeks of isolation are probably adequate. In homologous serum hepatitis the virus is not found in the stool so that isolation is unnecessary. However, there is no reliable method of distinguishing between the two types unless the incubation period is definitely known.

Both strains of the virus can be transmitted by parenteral inoculation of as little as 0.01 cc of infected blood plasma or serum. This danger is greatly enhanced by the presence in the population of a significant number of individuals (possibly 5 per cent) who carry the virus in their blood. In addition unrecognized mild acute cases may serve as donors. Nevertheless, most cases due to parenteral transmission are preventable.

At present no satisfactory method is available for sterilizing whole blood for transfusions although the use of nitrogen mustard is promising. A calculated risk must be taken and adequate indications must be present to justify the risk of hepatitis. Careful donor selection is helpful but does not eliminate the risk. Donors with a history of previous jaundice or of a recent acute illness should be rejected. A thymol turbidity and an icterus index can easily be performed with the routine Kahn test.

Pooled plasma and convalescent serum are

needles and syringes is readily prevented by autoclaving or adequate boiling. This includes equipment used to draw blood as well as that used to give injections. Special attention must be directed to the technique of capillary puncture for ordinary blood counts. The use of individual autoclaved or boiled knife blades is recommended. Ordinary alcohol sterilization is grossly inadequate.

Finally, the multiple dose per syringe method of administering such medications as penicillin or vaccines is dangerous. Infected serum may be drawn up when the plunger is pulled back to ascertain that the needle is not in a vein and thus contaminate the remaining doses.

Prevention of infectious hepatitis may also be accomplished by the administration of 10 cc of gamma globulin within 10 days after exposure. It is of no value after the appearance of symptoms. Such passive immunity is effective for about 11 weeks.

Active Treatment. The active treatment of acute infectious hepatitis and acute serum hepatitis is identical since they are caused by closely related strains of a filtrable virus and present essentially similar clinical pictures. Since at present there is no antibiotic or other specific substance available which is known to be effective against the virus, therapy is limited to supportive and symptomatic measures designed particularly to protect the liver cells and to aid in regeneration. However, it must be made clear as we have shown that proper treatment will sharply reduce the severity and duration of illness as well as the incidence of residuals and in some cases is lifesaving.

The principal pathologic lesion occurs in the liver and consists of injury to the parenchymal liver cells with a variable degree of necrosis and with associated inflammatory changes. Although this process is well established when symptoms first appear, it con-

tion explains why early treatment is so important. Acutely injured liver cells are peculiarly susceptible to additional noxious agents or procedures. But more important, it indicates why the maximal severity of the disease cannot be predicted until the crisis

cent glucose in normal saline should be administered by vein

The patient should be kept in bed for 24 hours. As soon as the nausea has subsided small amounts of fluid and soft light foods may be offered. Sufficient medication should be given for several days to prevent a recurrence of symptoms. During convalescence diarrhea may be controlled as in the milder cases.

RICHARD B. CAPPS

ACUTE INFECTIOUS HEPATITIS AND HOMOLOGOUS SERUM HEPATITIS

Prophylaxis. Acute infectious hepatitis is contagious through the fecal-oral route and consequently appropriate isolation measures are indicated. Only scant data are available regarding the persistence of the virus in the feces but in most cases 4 weeks of isolation are probably adequate. In homologous serum hepatitis the virus is not found in the stool so that isolation is unnecessary. However there is no reliable method of distinguishing between the two types unless the incubation period is definitely known.

Both strains of the virus can be transmitted by parenteral inoculation of as little as 0.01 cc of infected blood plasma or serum. This danger is greatly enhanced by the presence in the population of a significant number of individuals (possibly 5 per cent) who carry the virus in their blood. In addition unrecognized mild acute cases may serve as donors. Nevertheless most cases due to parenteral transmission are preventable.

At present no satisfactory method is available for sterilizing whole blood for transfusion.

justify the risk of hepatitis. Careful donor selection is helpful but does not eliminate the risk. Donors with a history of previous jaundice or of a recent acute illness should be rejected. A thymol turbidity and an icterus index can easily be performed with the routine Kahn test.

D. J. J. I.

needles and syringes is readily prevented by autoclaving or adequate boiling. This includes equipment used to draw blood as well as that used to give injections. Special attention must be directed to the technique of capillary puncture for ordinary blood counts. The use of individual autoclaved or boiled knife blades is recommended. Ordinary alcohol sterilization is grossly inadequate.

Finally the multiple dose per syringe method of administering such medications as penicillin or vaccines is dangerous. Infected serum may be drawn up when the plunger is pulled back to ascertain that the needle is not in a vein and thus contaminate the remaining doses.

Prevention of infectious hepatitis may also be accomplished by the administration of 10 cc of gamma globulin within 10 days after exposure. It is of no value after the appearance of symptoms. Such passive immunity is effective for about 3 weeks.

Active Treatment. The active treatment of acute infectious hepatitis and acute serum hepatitis is identical since they are caused by closely related strains of a filtrable virus and present essentially similar clinical pictures. Since at present there is no antibiotic or other specific substance available which is known to be effective against the virus, therapy is limited to supportive and symptomatic measures designed particularly to protect the liver cells and to aid in regeneration. However it must be made clear as we have shown that proper treatment will sharply reduce the severity and duration of illness as well as the incidence of residuals and in some cases is lifesaving.

The principal pathologic lesion occurs in the liver and consists of injury to the parenchymal liver cells with a variable degree of necrosis and with associated inflammatory changes. Although this process is well established when symptoms first appear it continues to progress during the preicteric stage and probably does not become maximal until some time between the appearance of jaundice and the onset of recovery. This situation explains why early treatment is so important. Acutely injured liver cells are peculiarly susceptible to additional noxious agents or procedures. But more important it indicates why the maximal severity of the disease cannot be predicted until the crisis

is past. Thus all cases must be treated as potentially severe until recovery has set in.

Our specific treatment in the different stages of the disease is as follows:

PREICTERIC AND ACUTE ICTERIC STAGES
Probably the most important single therapeutic measure in viral hepatitis as seen in civilian practice is bed rest. It should be instituted as early as possible, preferably at the time of onset of symptoms when the diagnosis is first suspected and not yet established. Bed rest should be continued for a minimum of 3 weeks or until convalescence is well advanced as indicated in a subsequent paragraph. If feasible, dietary privileges should be denied, particularly during the initial and acute stages.

The importance of the diet in civilian practice is difficult to evaluate. On theoretical grounds we believe that it is desirable to employ a moderately high protein (100 to 125 gm), high carbohydrate (250 to 300 gm), and a moderately low fat (60 to 80 gm) diet. If this diet can be taken, there is no evidence that the addition of lipotropic factors such as methionine or choline is of any additional value. In our diet the protein is largely beef and casein; the latter in the form of milk with a casein concentrate added and cottage cheese. Although the role of fat is not clear from a practical point of view, meat fat is poorly tolerated and a diet too low in fat is unappetizing. Thus we allow enough fat, mostly in the form of butter or butter fat, to make the diet appetizing.

In cases with nausea or vomiting persisting for more than a few days, it is desirable to provide protein and sugar by vein. This can be accomplished with amino acids, plasma or serum albumin, and daily intravenous injections of 1000 cc of 10 per cent dextrose in water.

The addition of vitamins is necessary only when nausea and vomiting are persistent. Excessive doses are undesirable.

In the early stages of the disease, fluids are of the greatest importance. From a symptomatic point of view, fluids should be forced either by mouth or by vein, 3000 to 4000 cc daily. This will usually result in a sharp abatement of symptoms, especially a decrease in or disappearance of nausea. Salt must not be given by vein unless vomiting is severe, since it leads to fluid retention. As

little as 3 liters of normal salt solution intravenously has been observed to produce ascites and large pleural effusions. It is desirable to restrict salt in the diet but any tendency toward fluid retention should be treated by a low salt diet.

Additional liver trauma is to be avoided. All drugs which are potentially hepatotoxic are contraindicated. Alcohol in any form must be strictly prohibited. Opiates and the short acting barbiturates, since they are normally excreted or detoxified by the liver, have a more prolonged action and more pronounced effect than in normal individuals and should therefore be used with caution. If at all, Atropine sulfate (0.4 mg) can be employed for abdominal cramps. Salicylates increase the prothrombin time and should be avoided in cases of severe liver injury.

During the initial and acute stages of viral hepatitis, even minor surgical procedures may be fatal. If surgery cannot be avoided, local anesthesia should be used, since most inhalation anesthetics are toxic to the liver.

Intercurrent infections are to be avoided and promptly treated. When specific measures for such complications are necessary, penicillin is definitely preferable to the sulfonamides. Finally, intercurrent diarrhea must be promptly controlled, if necessary by the use of 10 minims of deodorized tincture of opium three times daily. If constipation is present and requires medication, laxatives, especially saline cathartics, should not be used; some form of enema is preferable.

ACUTE LIVER FAILURE When the severity of the disease is such that acute liver failure develops, certain additional therapeutic measures are indicated. This situation is best recognized by a drop in the prothrombin level to less than 50 per cent of normal in the presence of an adequate amount of vitamin K, or by a drop in the urea nitrogen. Small daily doses (5 to 10 mg) of parenteral vitamin K should be given. Continuous oxygen is advisable. The possibility of hypoglycemia must be considered and, if found to be present, treatment with continuous intravenous glucose should be instituted. Hemorrhage due to decreased prothrombin, in spite of adequate vitamin K, can be controlled only by repeated small transfusions of whole blood.

CONVALESCENT STAGE The primary problem during the stage of convalescence is the question as to when the patient should be allowed out of bed. In our opinion this should not be done until the following criteria have been met

- (1) Icterus index normal for at least 10 days or, better, a normal prompt direct van den Bergh reading for 10 days,
- (2) An absence of subjective symptoms, especially anorexia, increased flatus, lassitude, and right upper quadrant and right lumbar ache,
- (3) Absence of liver tenderness on fist percussion and of tenderness in the right costovertebral angle, liver size approaching normal
- (4) Bromsulphalein dye retention (5 mg per kilogram dose) less than 5 per cent in one hour or 7 per cent in 45 minutes other liver function tests approaching normal

If only one of these criteria cannot be met, the patient can be allowed up after one extra week of bed rest. Caution must be employed in dealing with individuals over

40 years of age, cases with history of previous liver disease, or individuals who have had a particularly severe or prolonged illness. After being allowed up, patients should be observed for a period of at least 4 weeks. If during this time liver tenderness reappears, or if the laboratory findings become significantly increased, the patient should be returned to bed for a period of at least 3 weeks.

SUBSEQUENT TREATMENT Patients should not be allowed to return to strenuous work for a period of at least 2 weeks after getting out of bed, and preferably for a period of one month. Regular work can then be resumed, providing findings continue to be normal. Alcohol should be prohibited for a period of at least 3 months. It is probably best to maintain a reasonably high protein diet for this period.

RICHARD B. CAPPS

REFERENCE

- Capps R B and Barker M H. Management of Infectious Hepatitis. *Ann Int Med*, 26:405, 1947

DISEASES DUE TO BACTERIA

THE PNEUMONIAS

Since 1935 type specific antipneumococcus serum, sulfonamides of many types, penicillin, streptomycin, aureomycin and other less widely known agents have been added to the physician's therapeutic attack on pneumonia. Also a distinct shift in the incidence of the various types of pneumonia has occurred. It is now of much more than academic interest to diagnose accurately each patient with pneumonic consolidation as to etiology and extent of invasion and associated pathologic changes.

While many cases of pneumonia (or pneumonitis) are primary in the sense of being initial infections due to invasion of highly virulent micro-organisms, especially pneumococci and viruses, there are a great many others in which a particular set of circumstances makes it possible for micro-organisms leading a more or less saprophytic existence in the respiratory tract to invade the lung

parenchyma. Unless these predisposing conditions are recognized and combated along with active antibacterial therapy some failures will result.

In every case of pneumonia, whether hospitalized or cared for in the home, in addition to a painstaking history and physical examination, a careful bacteriologic examination of the sputum and blood prior to instituting

sable in estimating the extent of parenchymal involvement, especially in the early stages of all pneumonias. Often it too may be done in the home. A sudden onset with pleural pain, blood tinged sputum, and a chill, particularly if accompanied by leukocytosis and the presence of pneumococci in smears of the sputum is sufficient for the establishment of a working diagnosis of pneumococcus pneumonia and institution of therapy for that disease pending the results of sputum

and blood culture. On the other hand an insidious onset with scanty physical findings at the start scattered areas of increased density throughout the lungs as shown roentgenographically and a normal or decreased leukocyte count are strongly suggestive of one of the virus pneumonias for which antibacterial therapy can be expected to do no more than prevent secondary bacterial invasions.

Prophylaxis. NONSPECIFIC MEASURES

Awareness of the common predisposing conditions to the development of pulmonary infection is the first step in prevention. These conditions include among others (1) all infections of the upper respiratory tract particularly those due to the pneumococcus (2) those conditions which promote pulmonary congestion and underventilation such as cardiac decompensation heavy sedation particularly following operation nephritis with edema peritonitis shock from any cause poliomyelitis involving the respiratory muscles (3) pulmonary embolism (4) obstructive lesions in the bronchial tree (5) trauma to the thoracic cage (6) allergic pulmonary edema. The implications of the above considerations are obvious.

Value of Cultures of Nose Throat and Sputum. Smears and cultures of the nose throat and sputum and a leukocyte count are prerequisite to proper management of all respiratory infections whether pneumonia has developed or not. If these reveal large numbers of pneumococci hemolytic streptococci if *Streptococcus viridans* is found in the nose or if there is a high leukocytosis the indication for sulfonamide or penicillin in full doses is clear. *Hemophilus influenzae* and *Klebsiella pneumoniae* infections of the respiratory tract may respond better to streptomycin.

Prevention of Pulmonary Congestion. The necessity for prompt digitalization and oxygen therapy for patients with cardiac decompensation and for penicillin therapy if such patients have even mild colds is being better appreciated. In the same way senile and postoperative patients should not be allowed to lie passively in one position which combined with shallow breathing soon results in passive hyperemia of the lungs then bronchopneumonia. In addition to being forced to get out of bed at the earliest pos-

sible moment that their general condition permits such patients frequently benefit from 5 to 10 minutes of carbon dioxide administration every hour to promote hyperventilation.

Present interest in phlebotrombosis has made physicians aware of the need for prompt anticoagulant therapy when that condition is present or imminent and for the ligation of veins which have been the site of thrombosis as well as sulfonamide or penicillin therapy when pulmonary embolism occurs.

Removal of Bronchial Obstructions. The improvement following prompt removal of bronchial obstruction is so spectacular that it

dren the exudate in bronchi and bronchioles is so abundant and extensive that asphyxiation results from this mechanical interference with oxygen reaching the alveoli rather than from filling of the alveoli with fibrin plugs. In postoperative or postpartum aspiration of stomach contents or inhalation of foreign bodies severe pneumonitis is almost certain to follow if relief of the obstruction is delayed. Prompt bronchoscopic aspiration followed by antibacterial therapy is urgently indicated.

Prevention of Posttraumatic Pneumonia. Phillips has recently called attention to the high incidence of pneumonia following non-penetrating chest injuries. According to his figures 2 per cent of all primary pneumonia cases at the Permanente Hospital Foundation are posttraumatic. In the majority the consolidation developed at the site of trauma while in about 30 per cent it was at the site of the "contrecoup" pulmonary injury. When there is severe trauma to the chest Phillips recommends papaverine hydrochloride 30 mg and atropine sulfate 0.4 mg intravenously every 4 hours for 3 days following injury to prevent reflex pulmonary atelectasis. Relief of pain should be by procaine infiltration rather than by the use of sedatives and measures should be taken to in-

prophylactically are also important. These suggestions are timely and might well be

extended to all patients with severe injuries, particularly if they are elderly and have lain on the ground long enough to reduce body temperature. In such persons, it is always wise to delay any operative procedure that can be delayed until the potential post-traumatic pneumonia has been aborted.

Combating of Allergic Pulmonary Reactions In the management of highly allergic individuals known to be sensitive to feathers, dust, and other allergens, it is well to remember that such persons are often equally sensitive to bacteria. Therefore, if a bacterial infection initiates or accompanies severe allergic rhinitis or bronchial asthma, iodides in full doses to keep bronchial secretions thin enough not to occlude bronchioles, aminophylline to dilate the bronchioles, and antibiotics or sulfonamides to combat the infection are usually in order.

SPECIFIC PROPHYLAXIS While it is obviously impossible to produce specific active immunity against all of the micro organisms that may cause pneumonia, certain measures are distinctly helpful.

MacLeod and his associates and Walter Schenkein, and Suthiff have shown that a single subcutaneous injection of small amounts of the various specific polysaccharides of pneumococci produces a good immunity against these types of pneumococci but not others.

On the basis of reports of its efficacy in Army personnel, widespread immunization with vaccine prepared from influenza virus A and B has been accomplished in the United States. Among the few reports from responsible investigators have come indications that the incidence of influenza A and B and pneumonia accompanying these infections has been greatly reduced among the immunized persons. It is well to remind pa-

ministered in small desensitizing doses over a period of several months, has, at times, given welcome relief.

Active Treatment of Pneumonia At the present time, few patients who are even suspected of having pneumonia escape penicillin, aureomycin, or one of the sulfonamides. This procedure is defensible because practically all bacterial pneumonias are benefited by these measures, and in the virus infections probably some secondary bacterial invasion is prevented. However, since the kidney complications of sulfonamide therapy are common and other complications by no means rare, these drugs should not be continued for long periods unless the need for their use is clear. Complications of penicillin therapy are less serious, but allergic reactions to it are becoming more frequent. The difficulty of administration and the cost of the antibiotics also are considerations which cause one to weigh the need carefully before ordering them.

ANTIBIOTIC THERAPY *Penicillin* Penicillin is useful against all of the pneumonias caused by gram positive cocci, particularly pneumococcal pneumonia, and psittacosis. It may have some specific effect in the other ornithosis pneumonias, but actual proof is lacking. Also when one is in doubt as to the etiology, and bacterial pneumonia seems a strong probability, penicillin is the agent of choice. In older persons with hypertension or arteriosclerosis and in any individual with known renal impairment it should, if pos-

responses from its use.

At present there is widespread interest in developing the most convenient and economical dosage compatible with clinical effectiveness. In the near future some revision of present concepts may have crystallized enough to merit general acceptance. However, from present evidence the safest way to be sure of controlling bacterial growth in pneumonia is to administer the penicillin in aqueous solution, using a physiologic solution of sodium chloride as the diluent, in

two of the de termine. The author's own impression is that they are of distinct value in persons who possess bacterial allergy. In such persons who have repeated respiratory infection, an autogenous vaccine, made from streptococci pneumococci or *Hemophilus influenzae* cultures from the nose, throat, or sputum, ad-

fewest reactions, sulfadiazine is the sulfonamide chosen by most physicians. Sulfamerazine, its isomer, appears to be equally efficacious. The blood level of sulfadiazine can usually be maintained in adults at 5 to 10 mg per cent or above by 1 gm every 4 hours by mouth after an initial dose of 2 to 4 gm, but in occasional patients with excellent renal function, the dose must be higher. Of course, in others, too high a blood level is reached on this schedule and the dose must be decreased. In most cases requiring intravenous injection of the sodium salt, 2 gm every 6 hours or 3 gm every 8 hours are about right. Sulfamerazine is excreted more slowly. After an initial dose of 2 gm in the adult an effective blood level may usually be maintained by 1 gm every 8 hours by mouth though this dose at 4 hour intervals is usually well tolerated. When intravenous administration of the salt is required, 2 gm every 8 hours is usually adequate. These doses may be given directly into the vein in 5 per cent solution or added to a venoclysis of 5 per cent glucose in water or of physiologic solution of sodium chloride. When sodium salts of sulfonamides are added to alkaline solutions, the drug will be precipitated.

If sulfathiazole is the sulfonamide chosen, the dose must be larger. After an initial dose of 3 or 4 gm, the maintenance dose, early in the course of bacterial pneumonia, usually should be 1.5 to 2.0 gm every 4 hours if renal function is unimpaired. Even with this dose, it is sometimes impossible to maintain a blood level as high as 10 mg per cent, but a lower blood level is often effective. There

is one other factor which is usually emphasized, but it is sufficiently important to bear repetition. It still seems not to be well understood that large doses of sodium bicarbonate are required to keep the urine at a pH of 7.5 which is a fairly safe level. In our experience, 16 to 24 gm by mouth, per 24 hours is required, making an oral dose of about 30 gm every 4 hours. If the patient cannot take the alkali by mouth, he should receive 1 liter of $\frac{1}{2}$ molar sodium lactate solution every 24 hours by vein.

Recently a new sulfonamide, 3, 4 dimethyl-5 sulfanilamide isoxazole, which has been given the trade name of *gantrisin*, has been released for clinical use (Rhoads et al.) It has practically the same range of clinical usefulness as sulfadiazine and is given in the same dosage, but is many times more soluble in the urine. Unless the patient's fluid intake is inadequate, an alkaline adjuvant need not be given with it. It also has the advantage that its salt as the diethionalamine is not irritating and may be given intramuscularly in concentrations as high as 40 per cent solution. The writer's experience with this drug in bacterial pneumonia is limited. But if it proves as efficacious in large series of cases as the early work indicates, in time it probably will replace sulfadiazine and sulfamerazine because of its greater safety.

BIOLOGIC THERAPY Since the advent of sulfonamides and penicillin, specific antipneumococcic rabbit serum is seldom used. However, at the height of the interest in its use many dramatic cures were effected without any other antibacterial therapy. In desperate cases, if the pneumococcus can be typed and type-specific serum obtained it may be the factor which tips the balance in favor of recovery. In one case of hemolytic streptococcus pneumonia, scarlet fever convalescent serum in a dose of 200 cc intravenously appeared to be the factor which, in addition to sulfadiazine, produced a favorable outcome. In one of the writer's most severe cases of atypical primary bronchopneumonia, in which the issue was uncertain for several days, a blood transfusion from a patient recently recovered from this disease appeared to be a lifesaving measure. We have not used Alexander's *Hemophilus influenzae* serum in the pneumonias associated with this organism, but from experience with this serum in *Hemophilus influenzae* meningitis, one would be tempted to use it in a critical case if streptomycin were not controlling the infection. The writer has used staphylococcal antitoxin in only one case of staphylococcal pneumonia, without a favorable result. However, this agent is of some value and should be considered in patients failing to respond to penicillin and sulfonamides.

GENERAL MEASURES Of the general measures to be used in pneumonia, complete rest

in bed is probably the most important. Observations have shown that pneumococcal pneumonia patients properly treated are incapacitated for about one half the period as patients with viral pneumonia. The prolonged prostration which follows the latter type is probably its most serious feature. The exact time at which pneumonia patients may safely leave their beds and later resume their normal activities depends on the judgment of the physician in each case. It should never be before 3 full days without fever have elapsed. Many patients with primary atypical bronchopneumonia have been incapacitated for as long as 6 weeks. Those with bacterial pneumonia properly treated may at times be back at work 2 weeks after the onset.

Pulmonary Edema. One serious condition frequently appearing in respiratory infections and particularly pneumonia is the intense pulmonary edema which occurs suddenly in patients in whom previously the manifestations have been relatively mild. When this edema occurs because of a failing myocardium the situation is serious. Probably the somewhat outdated practice of phlebotomy should be used more often in these cases to reduce the load on the right heart. Even if it is not used, more care should be taken than is usually done to avoid increasing this load by giving large amounts of fluids intravenously and by guarding

against the possibility of decompensation. The digitalizing dose of

0.2 mg daily is usually sufficient. It is now well established that simple tachycardia of the type accompanying any severe infection is not in itself a reliable indication for digitalis.

When the pulmonary edema is due to an intense allergic reaction it is usually more easily controlled than when the cause is decompensation. Aminophylline 0.25 gm for adults administered slowly by the intravenous route usually gives the most prompt relief. This should be followed by potassium iodide in doses of 8 to 12 drops of the saturated solution three or four times daily and

aminophylline by mouth. If the patient is unable to take it by mouth 10 gm of sodium iodide in 10 per cent solution may be given intravenously. Adrenalin 3 to 5 minims of a 1:1000 solution subcutaneously of course gives prompt relief in bronchial asthma but there are more dangers of serious reactions in hypertensive and other cardiovascular patients than when intravenous aminophylline is used.

Oxygen Administration. Oxygen in dosage to the point where cyanosis is fully relieved

capillaries is greatest in "wet" pneumonias with large amounts of secretion in the bronchioles, particularly if circulation through the lungs is impaired by a failing heart. Also if consolidation is quite extensive cyanosis usually is present. The method of oxygen administration is a matter of individual preference. Introduction by nasal catheter is probably the most efficient and economical. Usually the catheter is put into one nostril far enough so that its tip appears just beyond the free edge of the soft palate. It is changed from one nostril to the other every 12 hours. The writer uses a modification of this technique suggested by Krasno. The catheter tip is inserted into a hole cut in the center of a small piece of sponge rubber which has been trimmed to fill one nostril snugly. The catheter is pushed only far enough so that the tip clears this rubber collar. Thus irritation from the catheter lying in the floor of the nostril is avoided. When

about 8 liters

For patients who do not tolerate the nasal catheter well the oxygen tent should be used. Unless a rubber sheet completely covers that portion of the mattress which forms the floor of the tent and the skirts of the tent are tucked under the mattress and bedcovers snugly, much oxygen will be lost. Usually a flow of about 12 liters per minute is required to maintain an oxygen concentration of 50 per cent which is considered desirable. The oxygen concentration should be checked every 8 to 12 hours so that the proper flow can be gauged if possible.

Meteorism Meteorism often proves to be a serious problem in patients who are extremely toxic. Prompt and abundant oxygen administration is the most efficacious way of combating it. In addition, hot stupes to the abdomen, enemas to empty the colon of feces, high rectal tubes through which gas may be expelled or siphoned off, and injection of prostigmine 1 cc of the 1:2,000 dilution are all measures which may help.

Control of Cough The cough of pneumonia may be a troublesome feature. It is part of the mechanism of ridding the bronchioles of exudate and should not be entirely suppressed. If the sputum is extremely thick and tenacious, potassium or sodium iodide in doses of 8 to 15 drops of the saturated solution in $\frac{1}{2}$ glass of water will reduce the viscosity appreciably. For a painful hacking cough, codeine sulfate or phosphate in doses of 30 mg. every 4 to 6 hours is the best remedy. It may be given in conjunction with elixir of terpin hydrate. A favorite prescription of the writers is

Syr. ipecac	} -aa	drams i
Syr. squill		
Morphine sulfate		grains ii
Elixir terpin hydrate		ounces vi

Sig. 1 Teaspoonful every 3 hours for cough

Codeine may be given separately in addition to this. It must be remembered that if more than two doses of codeine per 24 hours are required, constipation may become a problem.

Pleural Pain Pleural pain should, if possible, be relieved by aspirin or phenacetin compounds in the usual doses with the occasional addition of codeine. Heat to the affected area usually helps. If these measures fail, strapping the chest with adhesive may be required. This should be avoided if possible because it obscures the physical signs.

Dehydration Dehydration may become a problem in pneumonia because the patient may be too sick to call for water himself. Water or fruit juices or weak tea up to a minimum of 2500 cc. every 24 hours for adults during the febrile period should be insisted on. If the patient cannot take them by mouth, intravenous fluids may be required. When sweating has been quite profuse, 1 liter of physiologic solution of sodium

chloride or Ringer's solution may usually be given safely. The remainder of the day's requirements should be 5 per cent glucose in water or amino acids in glucose solution. *Fluids must be given slowly* because of the danger of increasing the load on an already overburdened heart.

Complications Of these empyema is probably the most common. When this condition is strongly suspected, thoracentesis should be done promptly. As much of the purulent fluid as possible should be aspirated and 50,000 to 100,000 units of penicillin introduced into the cavity before withdrawing the needle. If frank pus is present, surgical drainage after rib resection usually should be done. Occasionally, when treatment has been prompt, repeated evacuations through the needle along with penicillin in full doses will effect a cure.

ca or no often serve as the foci for metastatic lesions in the brain and meninges.

Bacterial endocarditis, usually pneumococcal when a sequel of pneumonia, is an extremely serious complication. When the diagnosis is established, doses of penicillin not less than 1,000,000 units per day given in equal doses every 2 hours day and night, should be used if the offending organism is penicillin sensitive.

For the rare endocarditis case due to gram negative bacilli, a correspondingly high dose of streptomycin is in order.

Pneumococcal or streptococcal meningitis as a sequel of pneumonia has been discussed in the following sections.

PAUL S. RHOADS

REFERENCES

- Blake F. G., Howard M. E. and Tatlock H. Feline Virus Pneumonia and Its Possible Relation to Some Cases of Primary Atypical Pneumonia in Man. *Yale J. Biol. & Med.*, 15: 139, 1942.
 Eaton M. D., Meiklejohn G. and van Herick, W. Studies on Etiology of Primary Atypical Pneumonia. Filtrable Agent Transmissible to Cotton Rats, Hamsters and Chick Embryos. *J. Exper. Med.*, 79: 649, 1944.
 Krasno L., Karp M., and Rhoads P. S. Inhalation of Penicillin Dust. *J. A. M. A.*, 138: 341, 1945.

- sular Polysaccharides *J Exper Med* 82 445 1945
- Leber A. F. Ecology of Psittacosis and Ornithosis (De Lamar Lecture) *Medicine* 21 175 1942
- Phillips E. Pneumonitis Following Nonpenetrating Chest Injuries Study of 56 Cases *Permanent Found M Bull* 3 112 1945
- Thoms P. S. Svec F. A. and Rohr J. H. Clinical Experiences and Laboratory Observation on a New Sulfonamide—Gautrisan (To be published)
- Madell J. E. Jackson E. M. and Harman J. W. New Virus Disease of Pigeons Recovery of Virus *J Exper Med* 81 385 1945
- Valter A. W. Schenkman E. L. and Suttiff W. D. Mouse protective Titers of Sera of Volunteers Following Infection of Pneumococci of Their Type specific Polysaccharides *J Exper Med* 83 321 1946
- Wechsler H. F. Rosenblum A. H. and Sills C. T. Infectious Mononucleosis Report of Epidemic in Army Post *Ann Int Med* 25 113 1946
- Wier J. M. and Horsfall F. L. Jr. Recovery from Patients with Acute Pneumonitis of Virus Causing Pneumonia in Mongoose *J Exper Med* 72 595 1940
- Wong S. C. and Cox H. R. Action of Aureomycin against Experimental Rickettsial and Viral Infections (To be published)
- Zachus J. and Shaughnessy H. J. Isolation of Apparently New Virus from 2 Fatal Pneumonia Cases *Science* 102 301 1945

MENINGOCOCCAL MENINGITIS*

which the meningococci find their way into the blood stream to attack the meninges

General Treatment Because this is the only form of meningitis designated as communicable the patient should be isolated

*At the time of this writing few reports indicating the value of aureomycin and chloromycetin in the treatment of bacterial meningitis have appeared. Evidence indicates that both of these antibiotics traverse the blood brain barrier and diffuse readily into the cerebrospinal fluid. For this reason it would seem likely that both of these agents may in the near future assume an important place in treating infections of the central nervous system.—*Editor*

and the case reported to the local health officer. Confinement in a darkened room is not necessary. Good ventilation is important, and the principles of medical asepsis are particularly essential during the first few days of illness. It is a good practice to have restraints on every meningitis patient. Sedatives are not always required but if they are morphine should never be used. Sodium phenobarbital or sodium amytal in doses appropriate to the age and condition of the patient is usually satisfactory. An ice bag to the head is sometimes helpful.

Drugs The sulfonamides are now universally used for therapy. Antisera are not likely to be available even if desired as adjuvants. Penicillin is not an important accessory for treatment of the ordinary form of meningococcal meningitis. Nevertheless with massive doses (1,000,000 units daily) recovery with penicillin alone is possible. It is useful for some of the complications. Penicillin should never be given intrathecally. Its introduction in this manner may result in disastrous consequences (Hoyne and Schultze) some of which recall earlier days when intraspinal serum was a routine procedure. Sulfadiazine is undoubtedly the drug most commonly selected while sulfanilamide rarely receives any consideration. Sulfapyridine has declined markedly in popularity, but sulfamerazine has some advantages not possessed by the other sulfa drugs. Warnings have been issued persistently by manufacturers of sulfathiazole (Hoyne and Grossman) and by others not to use this drug for the treatment of meningitis. The chief objection set forth is that sulfathiazole does not readily enter the cerebrospinal fluid. Nevertheless our experience has been that even though blood levels and consequently spinal fluid levels for sulfathiazole are lower than with any of the other sulfonamides the results of treatment are equally as good if not better. Combinations of the sulfonamides are also obtainable in tablets consisting of

sulfadiazine 37 per cent. Favorable and unfavorable opinions have been expressed in respect to their superiority over a single sulfonamide. Their purpose is to lessen the likelihood of damage to the kidneys.

The dose is usually determined on the basis of body weight, administering from 1 to 2 grains per pound, according to the severity of the infection. The estimated amount constitutes the total dose for the first 24 hours of treatment. The initial dose would then be one half the total, and the remainder divided into five equal parts, given at 4 hour intervals, until the drug is discontinued. This method of figuring dosage may be suitable for a child. However, it is apparent that in the case of adults it would often result in excessive estimates. Therefore it has been

weight of the patient. Even for an infant, our initial dose of a sulfonamide is seldom less than 5 gm followed by 1 gm at 4 hour intervals for 3 to 4 days and then reducing

those over 10 years the initial dose is generally 5 gm, irrespective of the sulfonamide selected. In extremely severe infections the initial dose is sometimes repeated after a lapse of 2 to 4 hours and rarely 2 gm are administered at 4 hour intervals for 2 or 3 days and then reduced to 1 gm until discontinued when the temperature has remained normal for about 48 hours. The average number of days for sulfonamide therapy is usually 5 to 8.

FLUIDS AND ALKALIES Before beginning sulfonamide treatment, it is well to administer fluids and to see that the patient receives from 500 cc to 3000 cc daily, depending on age and whether a state of dehydration is present. During the first few days much of

often placed on the necessity of an alkali when prescribing a sulfonamide. Sodium bicarbonate is usually given to each dose of the latter is sometimes estimated on the basis of 1 cc per kilogram of body weight. However, it has seemed to the writer that the

volume of fluid intake is of more importance than the alkali in preventing unfavorable reactions from the sulfonamides.

ROUTE FOR ADMINISTRATION OF SULFONAMIDES If the patient is an adult and rational the drug may be given orally. For infants and young children, oral administration is often unsatisfactory. The drug may not be swallowed or emesis may occur without the knowledge of the physician. As a consequence, the patient with no benefit from the drug fails to improve or rapidly loses ground. To avoid such possibilities, some physicians resort to gavage or adopt the stomach tube to which there are numerous objections. Sulfonamides have also been given by rectum, an unsatisfactory procedure. Two thoroughly reliable routes for giving sulfonamides when oral administration is not feasible are the intravenous and the subcutaneous. In either instance one can be assured that the drug will be retained.

At the Municipal Contagious Disease Hospital, Chicago, and for patients on my service at Cook County Hospital, the routine plan is to inject the initial dose of the sulfonamide intravenously. The sodium salt of the drug in 5 per cent solution is given in normal saline by the drip method. Almost any prominent vein is suitable for insertion of the needle, but a vein near the bend of the elbow, at the ankle, or the dorsum of the foot is usually selected. For the administration of an initial 5 gm dose of sodium sulfadiazine, the 5 gm will be in a flask containing 100 cc of normal saline, to make the 5 per cent solution of the drug. It will require about one hour for the patient to receive this treatment, the time depending on the rate of flow. Generally, allowance is made for 20 to 40 drops a minute. The arm or leg in which the needle is inserted should be firmly immobilized on a splint and the latter securely attached to the bed, in order that the needle does not become displaced or blocked by blood. The latter may happen if the flow is too slow. Frequent attention should be given to this matter. If the patient is in a comatose condition and continues so for several days, it may be necessary to repeat intravenous medication a number of times.

• 24 hours
• initial dose

sometimes it is difficult to pierce an infant's skin without a "cut down," a procedure often followed in our contagious disease hospitals. To circumvent this requirement, the sulfonamide can be injected subcutaneously with satisfactory results, even when given at 6 to 12 hour intervals. The sodium salt is used for subcutaneous injection as well as for intravenous and can be given in either a 5 per cent or sometimes only a 2.5 per cent solution.

A blood level should be obtained within 24 hours of beginning treatment. If more convenient a sample of blood may be sent to the laboratory much earlier. The first blood level following the initial treatment is likely to be higher than those that follow, but not always so. A reading of 20 mg per 100 cc of blood is often expected, and it is hoped that when sulfadiazine is the drug concerned that a level of from approximately 10 to 12 will be maintained. It is advisable to obtain two or three readings a week. When sulfathiazole is used it will be found that blood levels are generally consistently low. Sometimes levels for this drug do not exceed 4 and rarely rise above 8, but the patient progresses favorably, nevertheless. In many hospitals daily or frequent spinal taps are made in order to determine sulfa levels in the cerebrospinal fluid. However, it has been shown that spinal fluid levels range ordinarily from 50 to 70 per cent at most of the blood levels. Therefore, from a practical standpoint, lumbar punctures are not a necessity for such a purpose. Some clinicians also wish a daily determination of the sugar in the spinal fluid, because its rise or fall is valuable as a prognostic sign. With such a routine, variations in the spinal fluid cell counts may also be noted and the presence or absence of organisms determined. From a scientific standpoint it is interesting to

the physician should be able to assure himself from clinical signs, without contributory evidence from the spinal fluid, whether or not the patient is responding to treatment. A complete blood count should be made before beginning treatment and a white blood count obtained at least once a week. There should be also a daily urinalysis, including a

microscopic examination for blood and also sulfa crystals.

MENINGOCOCCEMIA Patients with a bacteremia are treated as described for the ordinary form of meningitis. All procedures are the same as for meningitis. The culture is clinical with one blood culture. If the blood culture has been secured or if meningococci have been obtained on smear from petechiae in the skin, a lumbar puncture is not essential.

Chronic meningococcemia without meningitis is a rare condition. If inadequately treated it may continue for several months with periodic showers of petechiae. The treatment is the same as for acute meningococcemia, although large doses of penicillin may be added.

NASOPHARYNGITIS If a known contact develops a "sore throat" it should be assumed, until proved otherwise that a meningococcal infection is responsible. Prompt institution of treatment may abort a serious illness before the organisms gain entry to the blood stream. One gram of sulfathiazole or sulfadiazine orally three times daily for 3 days may be sufficient.

FULMINATING FORM Many such cases are patients with the so called *Waterhouse-Friderichsen syndrome*, with massive hemorrhages into the adrenals. There may also be minute hemorrhages throughout the tissues.

regarded as inevitably fatal, a number of recoveries have been reported in recent years. One of the primary purposes of therapy for such infections is to combat shock. The patient should be wrapped in warm blankets and the foot of the bed elevated. An aqueous solution of adrenal cortical extract, 5 cc given intravenously for the first dose, is thought to be helpful. Doses of the same drug in amounts of 2 cc are then given intramuscularly from two to four times daily. Sodium sulfadiazine, 5 gm, or sodium sulfa-

also plasma should be used for a blood transfusion of 50 to 150 cc. If whole blood cannot be secured readily, plasma is a good substitute. If possible an oxygen tent should be used.

CARRIERS Known carriers seldom develop the disease because they are usually immune. Nevertheless they may transmit the infection to others. Therefore anyone proved to be a carrier should be isolated and treated with a sulfonamide until negative cultures have been obtained from the nasopharynx. Two gm of a sulfonamide twice a day for three days should be sufficient. When a meningococcal meningitis patient is found in a household it is likely that some or even all contacts may be infected even though none develops meningitis. But whether infection has actually occurred or not prophylactic measures should be adopted. Generally 5 gm of sulfathiazole or sulfadiazine orally twice a day for 3 days is satisfactory for protection.

COMPLICATIONS Since intrathecal therapy for meningococcal meningitis has been largely abandoned though involuntarily because of the sulfonamides complications have declined precipitously. Deafness and loss of vision which formerly were fairly common are now seldom observed when there is prompt diagnosis and early treatment. When deafness does occur it is generally bilateral and if complete there is small chance that hearing will ever be regained. There is no satisfactory treatment. However if some hearing remains marked improvement may eventually take place. Among 233 patients treated with antiserum intrathecally some years ago in one of our contagious disease hospitals there were 20 with complete loss of hearing. What is sometimes re-

doses of penicillin sometimes 500 000 to 600 000 units daily. It should be injected intravenously as well as subcutaneously. Krause has given penicillin for endophthalmitis by means of iontophoresis with good results. An effort should be made to keep the pupil dilated with atropine 0.25 per cent and 1 or 2 drops of 15 per cent argyrol in the eye daily may be of value. Panophthalmitis with destruction of one or both eye balls is extremely rare.

Arthritis is the commonest complication and suppurates only occasionally when the knee joint is involved. It can be treated by means of immobilization and salicylates.

Hydrocephalus formerly common in infants is extremely infrequent if there has been intrathecal therapy. Frequent lumbar punctures for drainage will not improve the condition. Endocarditis and pericarditis with effusion are both rare and likely to be fatal although we have had 2 recoveries from the latter.

Aside from bronchopneumonia and occasionally lobar pneumonia most of the other complications including brain abscess suppurative otitis media various forms of paralysis mental retardation and changes in personality are rare. With modern methods of treatment the duration of illness is shortened that decubitus ulcers are seldom encountered.

TOXICITY OF SULFONAMIDES Sulfadiazine is responsible for more hematuria than any of the other drugs considered here. It is also more likely to cause blocking of the ureters with crystals and produce anuria. Sulfamerazine has come next to sulfadiazine in our experience in the frequency with which it causes hematuria. Yet the total amount of sulfamerazine required to bring about recovery is less than with other sulfonamides. Sulfapyridine was accompanied by less hematuria than either of the preceding two drugs but gave poorer therapeutic results. Sulfathiazole caused about one third as much hematuria as sulfadiazine and there are usually fewer skin rashes than from sulfadiazine or sulfamerazine. Sulfanilamide is seldom used now for the treatment of meningitis but it is less irritating to the kidneys than the other drugs referred to. However there is often cyanosis and it may produce psychomotor disturbances. In our contagious disease hospital neither nausea nor vomiting has been a prominent manifestation of toxicity from any of the drugs named. The possibility of agranulocytosis should always be considered especially if the drug is prescribed for an unusually long period. The foregoing opinions concerning the sulfonamides are based on an experience with the treatment of approximately 1 500 patients.

COMMENT Except for the purpose of diagnosis intrathecal punctures are not required in connection with the treatment of meningitis. This is not because of the introduction of the sulfonamides and other antibiotics. As early as 1934 Hoynes at Cook

County Hospital, discontinued all intrathecal therapy for meningococcal meningitis and gave all antisera intravenously. With this method the fatality rates were equally as low as they are today with the newer drugs. Therefore, it seems to be evident that an important contributing factor in reducing mortality by means of the sulfonamides is the absence of intrathecal therapy.

In 1936, the writer reported 76 meningococcal meningitis patients with a case fatality rate of 11.7 per cent, treated with antiserum by the intravenous method exclusively. In 1948, Hoyne and Brown reported 727 patients with a fatality rate of 14.8 per cent, treated with sulfonamides, and only 22 of the number had any intrathecal therapy. The fatality rate for the group of 22 who received penicillin intraspinally in addition to sulfonamides was 40.9 per cent.

ARCHIBALD L. HOYNE

REFERENCES

- Hoyne A L. Intrathecal Therapy Contraindicated for Meningitis. *Illinois M J*, 94:295, 1948.
 Hoyne A L. Symposium on Advances in Clinical Medicine, Acute Infectious Diseases. *M Clin North America* 31:61, 1947.
 Hoyne A L. Improved Methods in Treatment of Meningitis. *Mississippi Valley M J* 66:7, 1944.
 Hoyne A L. Treatment of Meningitis with Sulfonamides. Presented before the Second Congress of the Mexican Society of Pediatrics. Mexico City, March 30, 1944.
 Hoyne A L. Advances in Treatment of Meningitis. *J Pediat* 19:778, 1941.
 Hoyne A L. Therapy of Cook County Hospital. *Therapy of Meningitis JAMA*, 117:1973, 1941.
 Hoyne, A L. Epidemic Meningitis. *JAMA*, 115:1852, 1940.
 Hoyne A L. Treatment of Meningococcal Meningitis without Intraspinal Therapy. *Nebraska M J*, 21:321, 1936.
 Hoyne, A L. Meningococci (Meningococcal Infection), *New England Arch Pediat*, 52:418, 1935.
 Hoyne A L. Meningococcal Meningitis. Importance of Intravenous Therapy. *Illinois M J*, 68:307, 1935.
 Hoyne, A L., and Brown, R. H. Seven Hundred and Twenty Seven Meningococcal Cases. *Analysis Ann Int Med*, 28:248, 1948.
 Hoyne A L. and Grossman A. Meningitis and Sulfathiazole. *Arch Pediat*, 62:241, 1945.
 Hoyne A L., and Schultz A. Multiple Attacks of Meningitis. Report of Case with Autopsy. *Am J M Sc*, 214:673, 1947.
 Krause A C., and Rosenberg W. Treatment of Metastatic Meningococcal Endophthalmitis, Report of Case. *Arch Ophth*, 32:109, 1944.

Lohrey, R. C., and Toomey, J. A. Epidemic Meningitis and Meningococcemia Treated with Penicillin. *J Pediat*, 28:80, 1946.

INFLUENZAL MENINGITIS

Hemophilus influenzae (Pfeiffer's bacillus) type B must not be confused with epidemic influenza, which is caused by a virus. The etiology of this infection and its route of invasion are extremely important from a therapeutic standpoint. Although clinical evidence of meningitis may become evident with a violent abruptness, there are sometimes warning signs to prepare the experienced physician for what may follow. At the onset of infection, difficulty in breathing caused by edema about the glottis and epiglottis may lead to a suspicion of laryngeal diphtheria or laryngotracheobronchitis. Moreover, it soon becomes apparent that emergency measures must be adopted to relieve impending asphyxiation. Signs of respiratory obstruction in infants and children under 5 years of age, should always lead one to think of the possibility of a type B *Hemophilus influenzae* infection, and under such circumstances a blood culture should be obtained. In many instances the organisms pass from the nasopharynx into the blood stream, but with prompt diagnosis and treatment the infection may be subdued without indications of the meninges becoming involved.

Under the circumstances set forth, emergency treatment may demand an immediate tracheotomy. If the edema about the glottis and epiglottis is not too marked, an intubation will occasionally suffice, if performed by an experienced operator. Streptomycin in doses of 100,000 micrograms should be prescribed at once and be administered intramuscularly at 3 hour intervals. In addition, it is well to give from 1 to 2 gm of sodium sulfadiazine in 5 per cent solution in normal saline intravenously by the drip method.

taneous, and it is often satisfactory to give the drug in this manner at 6 to 8 hour intervals instead of 4. For those who prefer, dosage of the sulfonamide may be determined according to body weight, which would call for from 1 to 2 grains per pound

for total dosage during a 24 hour period. The entire estimated dosage would then be divided into an appropriate number of equal parts according to the time intervals established for this medication.

Within 12 to 24 hours after having carried out the procedures described, evidence of meningeal irritation may develop, and it becomes apparent at once that the patient is suffering from meningitis. However, it must be remembered that meningitis may develop without any respiratory embarrassment. A lumbar puncture should be performed and the spinal fluid will probably be cloudy and a laboratory examination should disclose gram negative, pleomorphic *Hemophilus influenzae*. No additional intrathecal taps are likely to be required during the course of treatment. This statement is made notwithstanding the insistent advice to the contrary which has been given and continues to be repeated by clinicians with experience. As a rule, 5 days of streptomycin treatment should be adequate. However, the sulfonamide should rarely be discontinued in less than 2 weeks and a longer period may be necessary. For infants under one year of age it is also often well to administer intravenously by the drip method 50 to 100 mg of type II anti-influenzal rabbit serum. This serum may be given in from 50 to 100 cc of normal saline, to which are added 5 to 10 minims of adrenalin. It is particularly desirable to give

are likely to be at their height. When using type B anti-influenzal serum it is advisable to request the laboratory to make quelling tests with blood serum in order to determine if response to the antiserum is satisfactory. However, it is not imperative to perform quelling tests with cerebrospinal fluid. Consequently, there should be no occasion for making daily lumbar punctures for such a purpose. Nor are frequent spinal taps required with the object of determining whether there is a rise or fall in the spinal fluid sugar. If the patient is not responding well to treatment, transfusion of from 50 cc to 200 cc of whole blood may be of great benefit. If there is evidence of pneumonia or the patient is in a desperate condition it is advisable to inject intramuscularly ap-

proximately 30,000 units of penicillin at four intervals and place the patient in an oxygen tent. A few clinicians (Solovey) believe that penicillin may be of some therapeutic value in the treatment of influenza meningitis. This is undoubtedly true if the patient is treated intrathecally because the penicillin may combat secondary invaders if they are introduced by numerous lumbar punctures.

Complications. In most instances when convulsions occur it is during the first few days of the disease but rarely they may come on later. Chloral hydrate, 5 to 10 grains (300 to 600 mg) by rectum, may be helpful. Phenobarbital sodium, in doses of $\frac{1}{2}$ to 1 gram (30 to 120 mg), depending on the patient's age and the severity of the attack, sometimes proves to be satisfactory, if repeated when indicated. Other medications which may be used for the same purpose include secobarbital, $1\frac{1}{2}$ grains (90 mg), sodium amytal, 2 grains (120 mg), or ether inhalations. Magnesium sulfate in 25 per cent solution is sometimes effective when injected intramuscularly in 5 cc doses.

Facial paralysis, strabismus and paresis of one or more extremities are other complications for which there is no specific treatment. Generally such conditions improve progressively as the patient approaches recovery. Extreme irritability is noted more often in this kind of meningitis than in any other. In infants especially, mental retardation must be considered among the possibilities, if there are sequelae.

Toxicity of Drugs. It is well recognized that streptomycin may be responsible for certain toxic reactions. The most common is labyrinthine disturbance which usually disappears completely within a period of 3 weeks from the time that treatment was started. Deafness, often feared, is a much more serious complication because there is always uncertainty regarding the ultimate outcome in respect to regaining the hearing. If there is prompt discontinuance of the drug the chance of permanent impairment is lessened. Skin rashes from streptomycin are rare but indurated areas at the point of injection are not unusual. Chills, fever, nausea and vomiting have been observed. Renal damage is also said to occur rarely and has been attributed to unduly high levels of strep-

streptomycin, or in those receiving the drug intrathecally or in unusually large doses over a prolonged period Stomatitis (Beham and Ferr) has also been reported as a manifestation of streptomycin toxicity The frequency of hematuria as a result of sulfadiazine therapy has been discussed under the treatment of meningococcal meningitis The importance of adequate fluids has been stressed and the use of alkalis referred to It is impossible to state too emphatically that the intrathecal administration of streptomycin is not imperative for successful treatment of influenzal meningitis, and many admit the severity of its toxic reactions when given by this route Nevertheless, the Division of Medical Sciences of the National Research Council stated in January 1948 that, "Better results have been reported in patients with bacterial meningitis given streptomycin intrathecally as well as intramuscularly than in those receiving it intramuscularly only"

Those who persist in giving streptomycin intrathecally have reported fatality rates of 20 per cent and state that "Such excellent results emphasize the necessity for injecting streptomycin intrathecally" In referring to this mortality figure (20 per cent) in their recent book, Keefer and Hewitt also say "The necessity for administration of streptomycin both intramuscularly and intrathecally for the treatment of meningitis is well known" It is unfortunate that everyone does not know that intrathecal therapy is not required for the successful treatment of meningitis The same authors recommend intrathecal therapy for at least 4 to 7 days and "advisedly 10 to 14 days are necessary to obtain the best response to treatment and to prevent recurrences of meningitis due to occasional reinoculation of the meninges from intrameningeal foci which continue to harbor viable bacteria" This sentence is descriptive of what occurred when meningococcal meningitis was treated with serum intrathecally Hoyne and Brown reported 30 consecutive cases of influenzal meningitis with a fatality rate of 67 per cent Only 6 patients in the entire group received streptomycin intrathecally in addition to intramuscularly, and only 2 deaths occurred among those 6 Most of the 30 patients had but a single lumbar puncture, which was

performed for the purpose of establishing a laboratory diagnosis

All strains of *H. influenzae* are not positive for sulfadiazine, or to both In 1941, Hoyne reported 16 recoveries from influenzal meningitis There was no streptomycin at that time, nor was there available any sulfadiazine for these patients Seven of the number were given serum Three of those who had serum received no sulfonamides Six were treated solely with sulfapyridine 5 with sulfapyridine and sulfanilamide, and one exclusively with sulfanilamide Of the entire group it

of tuberculous meningitis Even at the beginning of the sulfonamide era, recoveries were few As late as 1940, Sirlin and London stated, "Until the present time only 5 cases

rate of 54 per cent

At present streptomycin is granted superiority over any other single agent for the

annual meeting of the American Academy of Pediatrics, held in November 1948, Alexander had an exhibit in which was shown a series of 30 patients treated exclusively with streptomycin Twenty two described as having mild or average attacks made good recoveries However, the 8 patients who had severe infections died Apparently, all pa

cally twice daily for 10 days and intramuscularly every 3 to 4 hours A sulfonamide was also given orally in "high doses" There were 12 deaths, a fatality rate of 40 per cent, and the author calls attention to the "high percentage of recoveries" given as 12, as 2 additional survivors had sequelae

Recently, Levinson reported 60 cases of influenzal meningitis treated according to different methods. Depending on the drug or combination of drugs fatality rates ranged from 100 per cent for 6 patients receiving sulfonamides alone, to no deaths for a group of 17 treated with streptomycin intramuscularly and sulfadiazine, but without any intrathecal therapy. He definitely decided that intrathecal streptomycin was unnecessary, thus confirming the contention of the writer.

Based on our own experience, and that of others, there seems to be no doubt that the treatment of choice for influenzal meningitis consists of both streptomycin and sulfadiazine. Moreover, it appears probable that each of these remedies can be administered at more extended intervals with satisfactory results. If such is the case, patients would suffer less discomfort and much time would be saved by the nursing service in a hospital. Even now it has been maintained that the total 24 hour dosage of intramuscular streptomycin can be given in a single daily injection without loss of the therapeutic effect gained from divided doses. Moreover, there are indications that 2 or 3 days' treatment with streptomycin will prove to be adequate in the management of influenzal meningitis when sulfadiazine is prescribed at the same time and continued for approximately 2 weeks. Consequently, efficient treatment may become still more simplified for those patients who do not receive intrathecal therapy. Nevertheless, because some strains of *H. influenzae* are resistant to streptomycin, it may become necessary to take advantage of type B anti-influenzal rabbit serum as an additional aid. If laboratory facilities are available, the sensitivity of *H. influenzae* to streptomycin and to the sulfonamide employed in treatment should be determined in every case.

With early diagnosis and prompt institution of appropriate treatment, the recovery rate for influenzal meningitis should now approximate 90 per cent.

ARCHIBALD L. HOYNE

REFERENCES

- Beham, H., and Perr, H. Stomatitis due to Streptomycin. Report of 11 Cases. *JAMA*, 138:495, 1945.
- Hoynes, A. L. Intrathecal Therapy Contraindicated for Meningitis. *Illinois M J*, 94:295, 1948.
- Hoynes, A. L. Advances in Treatment of Meningitis. *J. Pediat.*, 19:778, 1941.
- Hoynes, A. L. Epidemic Meningitis. *JAMA*, 115:1852, 1940.
- Hoynes, A. L. and Brown, R. H. Intrathecal Therapy Not Required for *H. Influenzae* Meningitis. Report of 28 Cases. *JAMA*, 136:597, 1948.
- Keeler, C. S., and Hewitt, W. L. Therapeutic Value of Streptomycin, a Study of 3000 Cases. Ann Arbor, Mich. J. W. Edwards, 1948.
- Levinson, A. Treatment of Tuberculous Meningitis with Streptomycin. *Proc. Inst. Med., Chicago*, 17:191, 1948.
- Lindsay, J. W., Rice, E. C., and Selinger, M. A. Treatment of Meningitis due to *Hemophilus influenzae* (Pfeiffer's Bacillus). Review of 103 Cases. *J. Pediat.*, 17:220, 1940.
- News and Comment. Intrathecal Use of Streptomycin. *Bull. U. S. Army*, 8:10, 1948. (Prepared for The Surgeon General by the Division of Medical Sciences, National Research Council.)
- Surlin, E. M., and London, A. H. Influenzal Meningitis, Case Report. *J. Pediat.*, 17:228, 1940.
- Solovey, G. Some of Our Observations on the Different Forms of Onset in Suppurating Acute Meningitis in Infancy. *Med. Woman's J.*, 55:35, 1948.

PNEUMOCOCCAL MENINGITIS

For many years the mortality for this form of meningitis approximated 100 per cent. Hewell and Mitchell reported that for 10 years preceding 1937 there were in the Children's Hospital in Cincinnati 23 cases of pneumococcal meningitis, all of which were fatal. During a period of 25 years the writer saw only 2 recoveries at the Cook County Hospital. However, when type-specific antipneumococcus rabbit serum became available the prognosis brightened. About 4 years later (1937) sulfanilamide was introduced, and with the broadening recognition which these two remedies received the number of deaths from pneumo-

..
treated during 1938 and 1939. Therapy consisted of the specific type of antipneumococcus serum intravenously and either sulfanilamide or sulfapyridine. This group of patients is mentioned particularly here because no intrathecal medication was given. Sulfapyridine appeared on the market shortly after sulfanilamide, and enhanced still further

ther a favorable outcome. Other sulfonamides have been introduced since, including sulfadiazine, sulfathiazole, and sulfamerazine, and any one of these singly or in combination may prove suitable for attack against the pneumococcus.

In 1941, Hoyne reported 14 recoveries. All but 2 of the patients received a specific type of antipneumococcus serum intravenously. Every patient was treated with a sulfonamide which was usually sulfapyridine. No patient received intrathecal treatment. Six patients each had but a single lumbar puncture, which was made for diagnosis. The largest number of spinal taps for any patient was four, which were done only in one instance. There were no recurrences or sequelae. The youngest patient was 5 years and the oldest 78.

Penicillin. Since the introduction of penicillin fatality rates for pneumococcal meningitis have declined considerably, but are seldom less than 50 per cent, and may be much higher for infants. Moreover, sequelae develop among those who survive. Hutchins and Davies reported 14 cases ranging in age from 6 weeks to 13 months. Treatment consisted of penicillin intramuscularly, 3000 to 5000 units every 3 hours, and intrathecally 10 000 units twice daily. This therapy was continued on an average of about 10 days. Type-specific serum was also given in 4 cases and sulfadiazine in 11. There were 5 fatalities and 4 were apparently cured. The remaining 5 had varying degrees of central nervous system damage. Ross and Burke had much better results with 19 patients treated with combined sulfadiazine and penicillin. Sixteen recovered with penicillin administered intrathecally as well as intramuscularly. The authors state that the penicillin produced no irritation. Sodium sulfadiazine with a dosage based on 2 to 3 grams (60 to 90 mg) per pound of body weight for each 24 hours was given at 8 hour intervals, in ½ molar lactate, 5 per cent dextrose in Hartmann's or in saline solution. Type specific antiserum was used routinely in the first 7 patients, but no conclusion is drawn regarding its value. Three of the surviving patients had residual central nervous system sequelae. One patient had relapses.

Intrathecal Therapy. Relapses and recurrences are not unusual with intrathecal

treatment and would undoubtedly occur more often with the use of penicillin alone than when combined with a sulfonamide. Boies expressed himself as favorably impressed by our method of treating meningitis without intrathecal therapy. He reported 3 cases of pneumococcal meningitis with recovery. One of the 3 had no intrathecal treatment. He states, "Because of the host of possible complications from multiple spinal taps emphasis is placed on a minimum number for diagnosis and therapeutic procedures."

Nearly all reported recoveries from pneumococcal meningitis have had intrathecal treatment. This route is often adhered to even though shock, convulsions, paralysis, and secondary infections lead to a form of meningitis that the patient did not originally have and even to death. Hoyne and Schultz reported a patient who had five attacks of meningitis over a period of approximately 5 years. A different organism was responsible for each episode. On the first four occasions the patient was successfully treated without intrathecal therapy. For the fifth attack penicillin was given intrathecally and after 4 days of such treatment an extensive subarachnoid hemorrhage developed, which was directly responsible for the man's death.

At the Municipal Contagious Disease Hospital (Chicago) during a 6 year period from 1942 through 1947 there were 68 admissions with pneumococcal meningitis. Thirty of the patients recovered without intrathecal therapy. This makes a fatality rate of 55.8 per cent which is not remarkable, but is equally as good as most similar series of patients which have been reported. The ages ranged from 2 months to 74 years. Eighteen of the

cocci. This entire group was treated without penicillin intrathecally and there were 14 recoveries. The authors make no reference to a previously reported large series of meningitis patients treated without intrathecal therapy. Nevertheless it is gratifying that they seem to have become convinced that meningitis patients can make good recoveries without intrathecal therapy. However, a lack

of confidence is displayed in the reliability of that plan because they believe "intrathecal penicillin should be reserved for those who do not respond to adequate systemic therapy."

Focus of Infection Before beginning treatment it is often not merely interesting but also important to determine the focus of infection. In many instances there appears to be no doubt that the ear is the port of entry for the pneumococcus. In others the primary focus is a bronchopneumonia or a lobar pneumonia. Just as with meningococcal meningitis, a large percentage of pneumococcal meningitis patients will have a positive blood culture. We have also observed on numerous occasions that patients with pneumococcal meningitis give a history of trauma about the head. Surprisingly often recovered patients have stated that they experienced a skull fracture, not recently, but one or more years in the past. Patients who have a skull fracture seem to be particularly susceptible to meningitis which is not always caused by the same organism. Two of our patients at the Municipal Contagious Disease Hospital who gave histories of having had fractured skulls experienced second attacks of pneumococcal meningitis, and on each occasion a different type of pneumococcus was cultured from the spinal fluid. At the Cook County Hospital we treated one man successfully on four occasions and he gave what appeared to be an authentic history of three previous attacks. This last named patient had his first attack of meningitis following a skull fracture which occurred in 1941 and his last hospital admission was in 1948.

Routine Treatment The routine treatment for pneumococcal meningitis need be no different from that for most other forms of meningitis. In every instance a blood culture should be obtained and a lumbar puncture made in order to establish a reliable

obtainable. Proper treatment demands adequate amounts of penicillin and one of the sulfonamides. As with other forms of meningitis, it is often well to administer the initial dose of the selected sulfonamide intravenously. For the average adult 5 gm of the sodium salt of sulfadiazine, sulfathiazole or sulfamerazine in a 5 per cent solution in normal saline can be given by the drip method, and the time required for this procedure will approximate one hour. The initial dose should be followed at 4 hour intervals, by from 1 to 2 gm, depending on the severity of the case. Ordinarily, 1 gm every 4 hours is sufficient. If the patient is rational and not vomiting the dose of sulfonamide may be given orally. Otherwise it may be necessary to continue the drug by vein. We believe there are objections to the use of a stomach tube for the introduction of the sulfonamide, and that resort to this method should as a rule, be avoided. In the case of children, either a 5 per cent solution or sometimes only a 2.5 per cent solution of the sodium salt of the drug can be given subcutaneously. With the subcutaneous route sufficiently high levels of the drug may be maintained when this medication is administered at intervals of 8 or 12 hours. This is especially true if sulfamerazine is the drug employed. Penicillin should be given in large doses, both intravenously and intramuscularly. Generally at least 25,000 units and possibly four times that amount may be injected intramuscularly at 8 hour intervals. In addition, from 200,000 to 500,000 units may be needed for intravenous administration every 24 hours for 2 or 3 days. Within 12 to 24 hours after the beginning of treatment it is advisable to determine the blood level of the sulfonamide, and this should be done two or three times a week. It is well to maintain a level of from 10 to 15 mg per cent for most of the sulfonamides. However, when sulfathiazole is used blood levels are likely to be much lower, and yet the patient progresses as favorably as when other sulfonamides are given and higher levels are obtained. The importance of adequate fluid intake and output must have critical attention at all times. An adult will usually require daily approximately 3000 cc of fluid parenterally. The question of giving an alkali should always be considered even

called in consultation to determine whether or not surgical intervention is indicated. There need be no delay in instituting treatment because the typing of organisms is no longer a necessity and a specific type of antipneumococcus serum is practically un-

though the quantity of fluid intake may be more important. For alkalization purposes equal quantities of sodium bicarbonate may be given with each dose of the drug when the patient is able to take oral medication. Otherwise, $\frac{1}{2}$ molar sodium lactate on the basis of approximately 20 cc per kilogram may be given intravenously daily.

Sometimes nothing is more effective for the patient who is making slow progress than a blood transfusion. The amount of citrated whole blood to be given will depend on the age and sometimes the condition of the patient. Generally the quantity will range from 50 cc for an infant to 500 cc for an adult. Plasma may also be used for the same purpose in corresponding doses. In addition glucose in either 5 or 10 per cent solution in distilled water or normal saline is likely to be a daily requirement.

As in other cases where a sulfonamide is prescribed, a complete blood count and urinalysis should if possible be made prior to starting treatment. Under any circumstances a white blood count should be made

sulfa crystals determined. If hematuria develops it is sometimes advisable to substitute a different sulfonamide should it be felt that

rted that

is readily

enters the cerebrospinal fluid, organisms disappear and patients make good recoveries without intrathecal treatment. It should be remembered that concentrations of substances in the spinal fluid are dependent on the concentration of those substances in the blood stream and the permeability of the barrier. Permeability of the barrier is increased during an attack of meningitis. Although in the past there was often much concern in regard to intracranial pressure and the demand that it be relieved by frequent lumbar punctures and drainage, much less thought is given to this matter now. Frequent lumbar punctures seem to stimulate the secretion of cerebrospinal fluid and headache is complained of more often because the intrathecal tap affords only temporary relief.

Treatment should be continued until the

patient is clinically well and the temperature has remained normal for at least 2 days. Many will desire an additional lumbar puncture for cerebrospinal fluid examination before the patient is discharged from the hospital.

PROGNOSIS An opinion regarding the outcome of the illness can often be formed following the initial and perhaps only lumbar puncture required when an examination of the spinal fluid is made. A high cell count with few organisms is favorable, whereas a low cell count with numerous organisms

though some clinicians desire daily lumbar punctures for frequent examinations of the cerebrospinal fluid in order to determine the sugar content in particular, such a procedure is by no means a necessity.

ARCHIBALD L. HOYNE

REFERENCES

- Boyes G J: Penicillin Treatment of Pneumococcal Meningitis. *Delaware State M J* 18:37 1946
- Hewell B A and Mitchell A G: Treatment of Pneumococcal Meningitis with Sulfanilamide. Review of Literature and Report of 6 Additional Cases. *JAMA* 112:1033 1939
- Hoyne A L: Advances in Treatment of Meningitis. *J Pediatr* 19:778 1941
- Hoyne A L and Schultz A: Multiple Attacks of Meningitis. Report of Case with Autopsy. *Am J M Sc* 214:673 1947
- Hutchins G and Davies J A V: Penicillin Treatment of Pneumococcal Meningitis in Infants. *J Pediatr* 27:505 1945
- Lowrey G H and Quilguth J J Jr: Treatment of Pneumococcal Meningitis without Intrathecal Penicillin. *J Pediatr* 33:336 1948
- Rhoads P S et al: Treatment of Pneumococcal Meningitis. *JAMA* 115:917 1940
- Ross S and Burke F C: Pneumococcus Meningitis in Infants and Children. Report on Use of Combined Sulfonamide and Penicillin Therapy. *J Pediatr* 29:737 1946

STREPTOCOCCAL AND STAPHYLOCOCCAL MENINGITIS

Streptococcal Meningitis: Sometimes it is difficult to realize that less than 10 years ago the prognosis of nearly every form of bacterial meningitis, with the exception of the meningococcal, was almost certainly hopeless. Sappington and Favorite, in a review of the literature in 1939, made the

comment, "Meningitis produced by the streptococcus pneumococcus staphylococcus influenza bacillus and tubercle bacillus is well as some rare organisms is almost universally fatal regardless of the treatment." Among the various forms of pyogenic meningitis streptococcal and staphylococcal organisms may be grouped with the lesser offenders. In a review of the literature to 1935 Gray found only 65 cases of reported recoveries from streptococcal meningitis and added his own case. However all of the recoveries that have been reported were not due to hemolytic streptococcus but included nonhemolytic as well. Presumably only a small portion of the total was due to *Streptococcus viridans*. However in an investigation of this subject by Hoyne and Herzon (unpublished) it has been interesting to note that in recent years at the Cook County Hospital while hemolytic streptococcal meningitis appears to be much less frequent than formerly the percentage of streptococcal meningitis which is due to the *Streptococcus viridans* is greater.

Recoveries from streptococcal meningitis have been so unusual (Felsen and Osofsky) that single instances were reported. Marick reported a nonhemolytic case in 1936 with recovery. His treatment consisted of spinal drainage every 8 hours for 4 days then twice daily for 5 days and then once. Since the sulfonamides came into general use the mortality from streptococcal meningitis has declined somewhat. Among Sappington and Favorites 22 reported cases of meningitis which were treated with sulfanilamide 8 were due to hemolytic streptococci and 4 of these recovered. There were also 2 instances of *Streptococcus viridans* meningitis with one recovery. Formerly whether with or without major surgical intervention entailing drainage there were usually numerous intrathecal punctures made for the relief of intracranial pressure and examination of the cerebrospinal fluid. On occasions blood transfusions and human convalescent scarlet fever serum were used in the hope of preserving life.

Streptococcal meningitis seems to occur more often by direct extension from a suppurating ear or mastoid infection than by way of the blood stream from a focus in the nasopharynx. The former route of invasion was on occasion noted in the past in our

contagious disease hospitals. Therefore when streptococci are found in the spinal fluid of a patient after a primary lumbar puncture the focus of infection should be sought in the middle ear or mastoid cells. Consequently under such circumstances it is advisable to have a consultant make a

preparation should be started. Sodium sulfadiazine 5 gm intravenously should serve well for the initial dose and be followed by 1 gm every 4 hours. The customary attention must be given to the use of alkalies and an adequate fluid intake. In addition 50 000 to 100 000 units of penicillin should be injected intramuscularly every 3 hours and perhaps intravenously as well. These patients may also benefit greatly from frequent blood transfusions. From 50 cc to as much as 500 cc of citrated whole blood may be given every other day if the patient's condition is extremely critical.

COMPLICATIONS If the patient survives the first few days of illness endocarditis may develop and its occurrence is sometimes announced by a shower of minute petechiae. If response to treatment with sulfadiazine is poor it may be advisable to resort to sulfanilamide which at times is particularly effective against streptococci. The dosage should be the same as for sulfadiazine. Rarely a brain abscess may occur or a lateral sinus thrombosis may be either an associated condition or else the primary focus from which

from which the meningitis develops. Notwithstanding the present armamentarium of modern drugs fatality rates in general continue to be high for this form of meningitis often approximating 50 per cent.

Staphylococcal Meningitis Staphylococcal meningitis is less frequently reported than most of the other pyogenic infections

from the laboratory that the organisms found are not a contaminant. Staphylococci should always be considered as the possible cause

sive blood culture in an aid in substantiating staphylococcal meningitis when staphylococci have been reported in the spinal fluid it suspected as a possible contaminant of the culture. A smear from the spinal fluid is less likely to be contaminated than a culture.

In general, treatment is the same for staphylococcal meningitis as when other organisms are responsible for meningeal signs. However, although favorable response may result from the administration of any one of the sulfonamides, sulfathiazole in this instance seems to be preferable. Penicillin could also be prescribed in large doses intramuscularly. In this manner from 50,000 to 100,000 units may be required every 3 hours and, in addition from 200,000 to 400,000 units intravenously daily by the drip method. Definite improvement is likely to be evident within 24 hours after beginning the treatment. There is no necessity for intrathecal therapy or frequent lumbar punctures or drainage. On two occasions I have seen recoveries brought about almost solely by means of numerous blood transfusions. In one of these instances, a 14 year old boy received blood intravenously on 23 occasions. Staphylococcus toxoid and staphylococcus antitoxin are of doubtful value.

In 1941, Hoyne reported 4 recoveries from

occurred in a baby 3 days old. Both spinal fluid and blood provided positive cultures for hemolytic *Staphylococcus aureus*. The infant was treated with sulfathiazole and penicillin and discharged from the hospital in good condition at the end of 16 days. There were no complications or sequelae after a period of 3 months. In so far as we could determine, this was the youngest patient ever reported with staphylococcal meningitis and the only one under 2 weeks of age who survived. The amount of sulfathiazole administered to this infant was 19 grains every 4 hours or approximately 0.8 gm. every 24 hours which was prescribed for 15 days. In this case, the dosage of the drug was based on the weight of the patient, administering about 2 grams

(60 mg.) per pound. Contrary to our usual custom for infants, the sulfonamide was given orally because the child had constant nursing attention and it was known that the drug was swallowed and retained. There were no overt reactions. Every 12 hours for a period of about 2 weeks, sodium penicillin in 5000 unit doses was injected intramuscularly. For the entire period of treatment the total amount of penicillin was 1,640,000 units, and the total dose of sulfathiazole was 15 gm. The highest blood level obtained for the latter drug at any time was 4.0 mg. per cent, which illustrates a previous reference pertaining to the low concentrations in the blood when sulfathiazole is the remedy. From the foregoing discussion it should not be assumed that staphylococcal meningitis is a condition found chiefly in children of tender age. As a matter of fact, although reported cases are not overnumerous, staphylococcal meningitis is likely to be observed more often in adults. Our oldest patient was a man of 70 years, who recovered.

COMPLICATIONS. With staphylococcal meningitis there is often a presumption that if the patient survives, osteomyelitis will make itself evident in some portion of the body. In reality, such a complication does not always occur. Among a comparatively small number of cases of staphylococcal meningitis the writer has seen only 2 who presented evidence of osteomyelitis. In one instance a small bone of the foot was involved, and in another there was an abscess formation in the shoulder joint with a probable osteomyelitis of the proximal end of the humerus.

ARCHIBALD L. HOYNE

REFERENCES

- Felsen J. and Ososky, A. G. *Streptococcus (111)* Meningitis with Recovery. *Immunologic Studies JAMA*, 103:2170, 1934.
- Gray, H. J. *Streptococcal Meningitis*. Report of a Case with Recovery. *JAMA*, 105:92, 1935.
- Hoyne A. L. *Advances in Treatment of Meningitis J. Pediat.*, 19:778, 1941.
- Hoyne, A. L., and Brown R. H. *Staphylococcal Meningitis Its Rarity in Newborn*. Review of Literature. Report of a 3 Day Old Infant with Recovery. *Arch. Pediat.*, 65:175, 1948.
- Marick S. W. Case of *Streptococcal Meningitis* with Recovery. *JAMA*, 106:2238, 1936.
- Sappington S. W., and Favorite G. O. *Sulfanilamide and Meningitis Ann. Int. Med.* 13:576, 1939.

TUBERCULOUS MENINGITIS

There has been perhaps no more amazing development in medical therapeutics than the discovery of an agent which is capable of retarding the progress of pathologic conditions caused by the tubercle bacillus. In the past tuberculous meningitis was almost certainly a fatal disease. It has been estimated that at least 50 per cent of infants and children who die of tuberculosis have tuberculous meningitis. As with other forms of meningitis, the condition is not primary. This fact is important from a therapeutic standpoint because other lesions in the body may require treatment as well as the meningitis. Infection of the meninges may take place through the blood stream or by direct extension from an osseous lesion in a locality contiguous to the circulation of the cerebrospinal fluid. In some instances it is believed that caseous tubercles in the brain substance may lie dormant for years before discharging bacilli into the cerebrospinal fluid. A large percentage of patients who die from tuberculous meningitis have primary tuberculosis.

Streptomycin Therapy. Schatz, Bugie, and Waksman's discovery of streptomycin reported in 1944 contributed the first real hope for the tuberculous meningitis patient. Standardization of streptomycin was reported by Waksman in 1945 but this antibiotic did not become generally available until 1946. Now favorable reports concerning this drug as an effective agent for the inhibition of tuberculosis are multiplying almost daily. But even with streptomycin extremely few claims have been made for permanent recovery from tuberculous meningitis.

Among 100 patients with tuberculosis reported by Bunn, 43 had meningitis without other evidence of tuberculosis. Sixteen of this number were living 4 to 7 months after starting treatment with streptomycin but only 4 had completely normal cerebrospinal fluid. Ten of the 16 patients showed no clinical evidence of meningitis. There were 10 patients who developed meningitis during or subsequent to treatment of primary tuberculosis. Only 3 of the 10 were living 11 to 12 months after the onset of meningitis and but one of the 3 could be classed as a

recovery. The daily dosage of streptomycin consisted of 0.6 to 4.0 gm intramuscularly and 0.01 to 0.2 gm intrathecally. Most of the patients were treated for 120 to 180 days. The author believes that 1.8 gm daily is advisable for not less than 90 days and that after 120 days the majority (two thirds) of the patients becomes streptomycin resistant. He states that a study of intramuscular versus intraspinal therapy for tuberculous meningitis has not appeared justifiable. The patients who responded poorly were those with a disseminated tuberculosis.

Alperin and Toomey reported 11 cases of tuberculous meningitis with improvement in 2. Two patients received streptomycin intrathecally and in one of these, three doses had little effect on the cerebrospinal fluid. All of the other patients were given streptomycin exclusively by the intramuscular route. There were 6 deaths. One of the survivors was blind. In another, the outcome was doubtful while in but a single instance the condition of the patient seemed to be good. Promin was also prescribed for all patients in this group.

Levinson treated 19 tuberculous meningitis patients with streptomycin intramuscularly. There was only one instance where the patient also received intrathecal treatment, which was continued for 9 days. Eleven of the 19 died at the time of the report, 8 were still living and improved. One patient was living 14 months after hospital admission. Levinson states "We have learned cerebrospinal fluid takes up streptomycin when given intramuscularly." The dosage consisted of 200,000 micrograms every 3 hours for 90 days. Deafness occurred in 2 patients. Although there was often quick response to streptomycin therapy, as a rule there was little change in the spinal fluid which required from 3 to 4 months to become normal. However, the spinal fluid glucose was sometimes normal within a few days. The Levinson test remained positive for 2 to 11 months. For those who progressed favorably the test became negative, but in those who did not improve the test was positive. Chlorides were not considered a reliable guide to recovery. Pulmonary tuberculosis which was present in 17 patients subsided in most cases. Streptomycin levels in the cerebrospinal fluid ranged from 40 to 160 micrograms.

notwithstanding that intrathecal therapy was not resorted to

Bertoye and Lantermer observed 11 cases in 3 of which there were encouraging results. In none of these patients was there an associated miliary tuberculosis. Nine of the patients were treated exclusively by intramuscular injections at first the dosage being from 15 to 1 gm daily later the dose was 0.5 to 0.25 gm according to weight. There was no improvement in one girl and one nursing who had received intraspinal injections of from 15 to 25 mg of streptomycin.

Since January 10, 1948, 12 tuberculous meningitis patients have been treated with streptomycin at the Municipal Contagious Disease Hospital (Chicago). The ages ranged from 5 months to 39 years. Nine of the 12 were less than 6 years of age. One was 13 and one 29. On December 15, 2 patients were still alive. One is a 2 year old Negro child who continues to be well nourished but is apparently blind and mentally deteriorated. The other is a 4 year old Negro girl whose condition seems to be good. Neither patient appears to have a disseminated tuberculous infection but there are pulmonary findings in the younger child. Tubercle bacilli were found in the spinal fluid of each patient. Both of these children received streptomycin intrathecally as well as intramuscularly. The younger child has been under treatment for 8 months and the older one for 11 months. The immediate future looks favorable for the latter whereas for the former the ultimate prognosis is undoubtedly bad. Our plan of treatment has been to administer approximately 1 gm of streptomycin daily in divided doses at 6 hour intervals intramuscularly for some patients and for others to give in addition 25,000 to 50,000 units intrathecally.

Given streptomycin by the intramuscular route exclusively all died. Nevertheless these figures are not a true indication of what may occur. One patient 39 years of age who received no intrathecal treatment died within 10 days; another without intrathecal treatment failed to survive throughout the day on

treatment was started and the other within 10 days. On the other hand a 9 month old infant who was treated exclusively by the intramuscular route survived for 7 months. Another patient 3 years of age who had no intraspinal therapy also survived for 7 months. At the Cook County Contagious Hospital the writer had a 14 year old Negro girl as a patient who had in addition extensive involvement of both lungs. She has been treated with streptomycin exclusively by the intramuscular route intermittently over a period of 14 months. Her present condition appears to be excellent. Roentgenographic examination has shown a striking recession of the tuberculous process in the pulmonary areas. Her mental condition is

had relapses on two occasions. During most of the time that streptomycin has been administered this patient has had approximately 15 gm daily in divided doses at 12 hour intervals.

BLOOD AND SPINAL FLUID LEVELS FOR STREPTOMYCIN. Ordinarily spinal fluid levels may be expected to range from 50 to 70 per cent of the blood level when there is no intrathecal therapy. For some of our patients who had exclusive intramuscular treatment with streptomycin spinal fluid levels were 25 micrograms when the blood level was 50. This ratio however was not true in all cases. Nevertheless in some instances spinal fluid levels were nearly double the blood level when the levels were obtained at the same time. Levinson reported spinal fluid levels ranging from 40 to 160 micrograms for patients who received no intrathecal therapy. A number of levels obtained from our patients who were treated intrathecally were far lower in comparison with the blood level than for certain other patients who had no intraspinal therapy.

Bunn who believes that treatment of tuberculous meningitis without intrathecal streptomycin is not justifiable, states that streptomycin is a local irritant and that intrathecal injection produces pain and on occasion paraplegia. He believes these phenomena are lessened by using slow well diluted injections of 50 mg on alternate days and that such treatment maintains

adequate concentration which should exceed 5 micrograms per cubic centimeter in the cerebrospinal fluid. Other reactions from streptomycin have been reported including fever and skin eruption when the latter occurs eosinophilia may be present. Among the more common toxic effects however are tinnitus, vertigo and deafness. Xanthochromic cerebrospinal fluid and agranulocytosis have also been reported.

DURATION OF TREATMENT Although Bunn believes as previously mentioned that the majority of patients become streptomycin resistant after 120 days I have seen one patient treated for 5 months continuously who relapsed after streptomycin was stopped but responded well when the drug was resumed. Just how long a patient should be treated with streptomycin is difficult to determine because relapses are so frequent. However if the patient appears to be clinically well and the spinal fluid has returned to normal it seems reasonable to stop medication but to keep the patient under observation.

Management of Patient The following procedures should be adopted: thorough physical examination, complete blood count, sputum examination, urinalysis and roentgenogram of chest. It is also well to have a laboratory examination of stomach washings and to do a tuberculin test. A lumbar puncture should then be made and an examination conducted in the laboratory for detection of tubercle bacilli. If the organisms are found a guinea pig inoculation should be performed. It would seem that although a sufficient number of patients has not been treated to provide adequate proof there is no necessity for giving streptomycin intrathecally. The intramuscular dose for patients under our supervision has varied from 1 to 2 gm daily. In some cases the total daily dosage has been divided into equal parts in order to give the streptomycin at 6 hour intervals. Nevertheless a satisfactory response has been obtained when the daily quantity of streptomycin was administered intramuscularly in two equal parts at 12 hour intervals. Some clinicians believe that the entire daily dose may be given in one injection. Para-aminosalicylic acid has been recommended as a substitute for streptomycin if the latter drug failed to produce a favorable

response. Sometimes para-aminosalicylic acid is given in addition to streptomycin. Pamisyl, which is manufactured in 0.3 gm tablets is a trade name for para-aminosalicylic acid. The daily dosage of pamisyl is 12 to 15 gm orally for an adult or 1 gm per 10 lbs of body weight for children. Dihydrostreptomycin hydrochloride which is derived from streptomycin by reduction is claimed to be a potent antibiotic. It is said to be as effective as streptomycin but much less toxic, and therefore can be prescribed in larger doses for longer periods. It is stated further that patients allergic to streptomycin have been able to continue with dihydrostreptomycin. This drug is stable at room temperature for one month and in powder form for 18 months. In solution it can be administered in doses of 250 to 500 micrograms per cubic centimeter. The minimum interval for intramuscular injections is 6 hours but 12 hour intervals are regarded as preferable. Not more than 2 cc should be injected at any one time and two injections in succession in the same general area should be avoided. The dose for children is 20 micrograms per pound of body weight. Dihydrostreptomycin is said to be less neurotoxic and responsible for less vestibular and auditory dysfunction than streptomycin. Moreover this drug rarely causes renal irritation and gastric disturbances.

The following diagram illustrates the method of combining streptomycin with a surface active agent. He states "By incorporating the known tuberculostatic agent on one end of a surface active molecule an increased *in vitro* effect on the tubercle bacillus has been obtained." He says further "It is anticipated that the more potent tuberculostatic drugs such as streptomycin could be made more effective by incorporating the molecules into a surface active compound."

In the brief period during which streptomycin has been employed for the treatment of tuberculosis the drugs accomplishments have been remarkable. However in respect to the therapy of tuberculous meningitis far more progress must be made before we can assume that patients with this disease will have even a fair chance for permanent recovery.

ARCHIBALD L. HOYNE

REFERENCES

- Alperin L. and Toomey, J. A. Treatment of Tuberculous Meningitis *J. Pediat.*, 33:74 1948
- Bertoye P. and Lantermier, J. Tuberculous Meningitis and Streptomycin *Rev. mens. de pediat.* p. 451 1949
- Bunn, P. A. One Hundred Cases of Miliary and Meningeal Tuberculosis Treated with Streptomycin *Am. J. M. Sc.*, 216:288 1948
- Eiseman B. A Means of Increasing the Tuberculostatic Effect of Known Chemotherapeutic Agents *J. Exper. Med.*, 83:189 1943
- Hoyne, A. L. Intrathecal Therapy Contraindicated for Meningitis *Illinois M. J.*, 94:295 1943
- Hoyne, A. L., and Brown, R. H. Intrathecal Therapy Not Required for *H. Influenzae* Meningitis Report of 23 Cases *J. A. M. A.* 136:597 1948
- Levinson A. Treatment of Influenzal Meningitis *Illinois M. J.* 94:227 1949
- Schatz A., Bugie E., and Waksman S. A. Streptomycin Substance Exhibiting Antibiotic Activity against Gram positive and Gram negative Bacteria *Proc. Soc. Exper. Biol. & Med.* 55:66 1944
- Waksman S. A. Standardization of Streptomycin *Science*, 103:40, 1943

SCARLET FEVER

Aim of Treatment The work of Lancefield and his co-workers, by their exact grouping and typing of hemolytic streptococci has thrown light on the epidemiology of scarlet fever. The causes of the complications, relapses, and reinfections are now clearly understood.

Gradually it has been realized that a hemolytic streptococcal invasion of the nasopharynx without a scarlet rash differs in no essential respect from a similar hemolytic streptococcal invasion with a rash. The hemolytic streptococci which elaborate an erythrogenic toxin are necessarily not more virulent than the same type of organism which does not produce a rash.

It has become apparent that poststreptococcal nonsuppurative syndromes such as rheumatic fever, glomerulonephritis and rheumatoid arthritis, follow the hemolytic streptococcal invasion of the nasopharynx in approximately 5 per cent of such infections. The known antigenic properties of the type-specific substance derived from group A hemolytic streptococci and the production of enzymes such as hyaluronic acid and hyaluronidase by these same organisms have brought about a realization that early and effective treatment is necessary.

Treatment must, therefore, be directed toward ridding the throat of the invading organism before quantities of the antigen are absorbed, and before complications, reinfections, and relapses can occur. Complications such as otitis media, may result from the primary organism. Relapses and reinfections are known to follow a change in the type of the pathogenic organism.

Treatment must also be aimed at blocking the antigen before the hyaluronidase (spreading factor) can carry the antigen into the mesenchymal cells. If the invading organisms can be destroyed before large quantities of the antigen or enzyme and coenzymes are produced, and before a change in type takes place, the patient will be spared the suppurative complications, such as otitis media and mastoiditis as well as the nonsuppurative complications such as rheumatic fever and acute glomerulonephritis.

Isolation Every case of hemolytic streptococcal invasion of the nasopharynx should be isolated. The cases of sore throat which, either before or during an epidemic, show

isolated until the throat culture can be reported upon. Those patients with positive throat cultures should be isolated. Treatment in a common ward is undesirable, irrespective of the type of organism, stage of the disease, and possible complications. Isolation is carried out in separate rooms in the hospital or private rooms at home. The hemolytic streptococci are air borne, and attendants and nurses must wear nasal and mouth masks. Bedclothing is oiled and all surfaces kept clean with oiled dust cloths. Individual thermometers and dishes are used, and sterilized after use.

Bed Rest All cases of scarlet fever are

rest is 3 weeks. Severely ill patients may require much more time in bed, determined by the degree of fever, heart rate, leukocyte count, sedimentation rate, and, if nonsuppurative complications are suspected, the electrocardiogram and the antistreptolysin O titer.

Fluids are forced by mouth up to 3000 cc daily. If necessary to maintain this amount parenteral routes may be chosen.

The diet is liberal, high in calories, proteins, and vitamin content. The form depends upon the patient's degree of toxicity.

Specific Therapy. Penicillin is the drug of choice.

Penicillin given in 150,000 to 300,000 units twice daily as advocated by Jersild or 300,000 units twice daily as suggested by Massell will free the patient's throat of streptococci in 24 to 48 hours. This dosage is continued for at least 6 and preferably 10 days. The patients treated for too short a time may have a recurrence of the infection since only small amounts of antibody are formed owing to the early eradication of the organisms. With penicillin therapy the average febrile period is 4 to 5 days instead of the 7 to 8 days in sulfonamide-treated patients. The rash of scarlet fever is uninfused by seen with spondyloarthritis.

per cent coming to surgery. In the sulfonamide group 21 per cent of the complications come to surgery.

Penicillin therapy permits home treatment of scarlet fever patients since oral penicillin 600,000 to 1,000,000 units per day is as effective in most cases as the intramuscular injection. Carriers of streptococci in the home should be subjected to the same type of therapy.

Sulfonamides in the form of sulfadiazine may be given to prevent the complications of scarlet fever. They are best used in conjunction with scarlet fever convalescent serum. Oral dosage of 1 gm per day to infants, 2 gm for older children and to young adults 0.5 gm every 8 hours with equal amounts of sodium bicarbonate and large amounts of fluid are adequate doses.

Scarlet fever antitoxin is of no real value. 0.2 cc injected intradermally will cause the rash to blanch (Schultz-Charlton reaction).

Pooled convalescent serum may be used in the highly toxic cases. The serum may be obtained from state boards of health in emergencies. The dosage varies from 10 cc intravenously in children to 60 cc intravenously in adults taking precautions against reactions.

Complications. The treatment of the suppurative complications is unnecessary because most of the complications are avoided by penicillin therapy. In 2 per cent of cases surgery may be necessary.

Desquamation. No treatment is necessary except to give comfort. If pruritus occurs use petrolatum to the skin or a mixture of 4 parts olive oil to 1 part glycerin in dilute alcohol.

Sore Throat. The sore throat requires no treatment if penicillin is used. In severe cases that are seen late a warm saline gargle and saline swab applied to the nose are all that is required.

Otitis Media. Otitis media sinusitis and

should be performed.

Nephritis. Nephritis usually occurs in the second to fourth week. If the case is seen late and penicillin has not been used examine the urine daily for albumin and red blood cells. When nephritis is discovered prolonged bed rest, a low protein, salt-free diet and avoidance of chilling are indicated. Of course every effort should be made to clear up the carrier state of the throat by using penicillin therapy.

Carditis and Arthritis are best treated if one remembers that the complications of scarlet fever are part of the rheumatic fever syndrome and appropriate treatment for rheumatic fever is instituted promptly.

Summary. The treatment of choice for scarlet fever consists of the early recognition of the etiologic organism and treating it promptly with bed rest, adequate diet and fluids and the prompt administration of penicillin for a minimum of 6 days, preferably 10 days. Aspirin is indicated as a blocking agent throughout the early part of the illness. Prophylactic immunization is of little or no value.

GEORGE C. GRIFFITH

REFERENCES

- Jersild T. Penicillin Therapy in Scarlet Fever and Complicating Otitis. *Lancet* 1:671, 1948.
 Massell H F, Dow J W and Jones T D. Orally Administered Penicillin in Patients with Rheumatic Fever. *JAMA* 133:1030, 1948.
 Rantz L A, Boisvert P J and Spink W W

Etiology and Pathogenesis of Rheumatic Fever

Arch Int Med 76 131 1945

Swift H F Wilson A T and Lancefield R C
Typing Group A Hemolytic Streptococci by M
Precipitin Reactions in Capillary Pipettes *J Ex
per Med* 78 127 1943

RHEUMATIC FEVER AND CHOREA

In recent years the increase in medical knowledge has led to a holistic or totalistic concept of diseases. Rheumatic fever is not a distinct disease entity. From the etiologic standpoint rheumatic fever is a poststreptococcal disease, a nonsuppurative complication of an invasion by one or more of the subtypes of group A streptococci (Rantz et al). From the pathologic standpoint rheumatic fever is one of the great group of collagenous diseases (Rich and Gregory). It is believed that rheumatic fever results from an antigen (derived from the streptococcus) spreading with the help of enzymes and coenzymes (such as hyaluronic acid and hyaluronidase) into contiguous mesenchymal structures. Since the arteries, arterioles and capillaries are the contiguous structures, rheumatic fever is characterized by arteritis. Because the collagenous degeneration of the vessels may be abrupt, the terms "anaphylactic" or "hypersensitivity" are applied. The multiple system manifestations result from the location of the involved vessels at a given time. Thus chorea is clinical evidence of active arteritis in the central nervous system as shown by Costero and associates; carditis is evidence of arteritis in the myocardium, pericardium and endocardium; pneumonitis is evidence of arteritis in the pulmonary vessels; and polyarthritides is evidence of arteritis in the synovial membranes of the joints.

Aim of Treatment. The aim of treatment of rheumatic fever therefore should be five fold:

- (1) To prevent streptococcal epidemics
- (2) To terminate a streptococcal invasion in the nasopharynx quickly in order to lessen the amount of antigen absorbed into the circulating fluids
- (3) To block the antigen which is absorbed from spreading into mesenchymal cells and prevent the collagenous degeneration
- (4) To marshal all of the available therapeutic armamentarium so that little

permanent damage results from the active inflammatory stage of the disease thus preventing crippling heart disease.

- (5) To teach the patient and family a way of life so that recurrent attacks will be prevented and the patient with serious heart disease can be a useful citizen in the community.

These objectives are broad and perhaps idealistic but without them little will be accomplished in the prevention of crippling rheumatic heart disease.

Prevention of Epidemics. It is a known and accepted fact that rheumatic fever epidemics follow epidemics of streptococcal throat infections. Paul Jones, Rantz and many others have demonstrated this fact. The most recent example is the experience of the Army in Japan and Korea in 1947 where epidemic streptococcal throat infections were followed by rheumatic fever in 29 per cent and 31 per cent of cases respectively (Griffith). An epidemic applies to a home as well as to a community or an army. Every case of streptococcal infection of the nasopharynx, no matter what the clinical manifestations are, whether it is an acute nasopharyngitis, a follicular tonsillitis or scarlet fever, should be isolated in the home in a private room, or in an infectious ward. Measures to prevent the spread of the infection must be instituted such as the wearing of face masks by all attendants, washing

with soap and water each hour is considered as a seedbed of an epidemic; the spread of streptococcal epidemics will be lessened.

Termination of the Infection. The streptococcal infection of the nasopharynx should be terminated as quickly as possible. In this manner the amount of antigen absorbed is lessened, specific type change of organisms will be prevented and the likelihood of an attack of rheumatic fever greatly reduced as shown by Massell.

The ideal treatment of the acute streptococcal sore throat is by penicillin either orally in 600,000 units daily or a similar dosage parenterally. This treatment should be continued for 10 days to insure against

reactivation of the infection or an invasion

bodies are formed. The use of sulfonamide drugs, such as sulfadiazine, is not as successful as penicillin (Hoyne and Brown, Meads et al.) and convalescent serum (Hirsh et al.). Sulfonamide drugs tend to increase the tendency to the development of the collagenous complications. Convalescent serum is attended with the danger of serum sickness, infectious hepatitis, or both.

Therefore, the aim of treatment in every case of streptococcal invasion of the nasopharynx is quick termination of the infection in order to prevent poststreptococcal complications, such as rheumatic fever.

Blocking Agents. During the growth and reproduction of the streptococcal organisms in the throat, toxic substances are absorbed by the lymphatics in the nasopharynx. These substances are antigens which circulate in the blood stream. The spreading factor, of which the best known example is hyaluronidase, causes these antigenic substances to penetrate the mesenchymal cells. The first mesenchymal structures which the antigens contact are the arteries, arterioles,

degeneration of these structures be prevented. Normally the protective mechanism of the body by antigen stimulation of antibody formation goes on unopposed, but in those patients where large amounts of antigen, enzymes and co-enzymes of the spreading factor type are present, nonsuppurative, inflammatory reactions in the mesenchymal tissue may occur. It is important, therefore, to block the antigens from penetrating the mesenchymal cells. Guera has demonstrated that tissues saturated with salicylic acid are not penetrated by antigenic substances, or at least the penetration is definitely delayed. Kyser and his co-workers have been able to show that animals which are well saturated with benadryl do not readily develop rheumatic-like lesions after receiving injections of a foreign substance, such as horse serum. Knowing, therefore, that the salicylates prevent or slow down the spreading factor, it is logical to assume that giving large amounts

of the salicylates at the time of the streptococcal invasion of the throat, and for 6 to 8 days thereafter, will help to block the penetration of the antigen into the mesenchymal cells, and thus prevent the development of poststreptococcal nonsuppurative complications, such as rheumatic fever. It is believed that the older physician, who treated his patients with large doses of the salicylates during and following a streptococcal throat infection, did much to prevent the development of rheumatic fever. The best blocking agent so far found is salicylic acid. It is wise to give a patient with a streptococcal sore throat 1 gram of acetylsalicylic acid per pound of body weight per day until the patient has fully recovered from the throat infection and the danger of a poststreptococcal, inflammatory reaction, such as rheumatic fever, has passed.

Available Therapeutic Armamentarium. Once rheumatic fever has developed, the main objective of the physician is to terminate the rheumatic fever as quickly as possible and, during the course of the rheumatic fever, prevent crippling heart damage, if possible. Since there is no specific treatment for rheumatic fever, it is important that all available armamentaria be utilized to prevent prolonged morbidity and crippling heart disease. It has become the theme of public health agencies to emphasize the dire effect of rheumatic fever. Instead of implanting fear of a fatal outcome or fear of crippling heart disease in the minds of the patient and the family of the patient, I believe it is much more desirable that the physician point out that, with proper care, much can be done to prevent the serious crippling heart disease which has been so greatly feared. It is true that only 1 out of 2 children who develop rheumatic fever with heart disease live to the age of 40. It is known, however, that if a child has only one attack, and escapes serious heart damage, 90 per cent of the patients who reach the age of 21 or more are able to carry on normal activity without circulatory symptoms. Therefore, the aim of the physician who recognizes the primary attack of rheumatic fever is to direct the care of this patient so as to prevent crippling heart disease during the primary attack, and thereafter to prevent recurrent attacks, since reactivation of rheu-

matic fever most frequently causes serious crippling heart disease

The Treatment of Suspects Every patient with a hemolytic streptococcal sore throat is a potential rheumatic fever subject especially if he comes from a family with a rheumatic background or if he has had previous attacks of streptococcal throat infections. It is imperative therefore that this patient be observed over a sufficiently long period to detect the onset of an active rheumatic state at the earliest possible moment. A patient who is slow in recovering from the acute hemolytic streptococcal throat infection who is pale irritable nervous has a lessened span of attention and concentration runs a low grade fever and on study is found to have an elevated antistreptocolysin titer and perhaps an elevated sedimentation rate should be treated as a potential rheumatic fever patient. As stated above the throat infection should be cleared as promptly as possible with the use of penicillin. The patient should be given aspirin in the dosage of 1 grain per pound of body weight per day until the above mentioned symptoms and signs have subsided and until the physician is sure that carditis has not developed. The patient who has developed rheumatic fever either of the fulminating or of the polycyclic or low grade continuous type should be placed on a therapeutic regimen modeled somewhat after the following plan.

Rest Rest in bed is imperative for the patient with rheumatic fever throughout the entire stage of rheumatic activity. In the acute fulminating type where there is high fever and red hot swollen joints together with evidence of myocardial involvement the patient should be kept quiet in bed. Instructions to remain quiet are usually not necessary because the patient is so ill that he only moves on command. He is restless sleepless and irritable but he does not move about physically in the bed. However as soon as the patient becomes comfortable it is necessary to continue the bed rest and

is readily induced. Diversional facilities must be provided so that boredom and introspection are avoided. As the pain and general discomfort subside rest must be judiciously proportioned to the stage of rheumatic activity. Deep breathing exercises are instituted as soon as the patient is comfortable. Follow

when these exercises can be accomplished without an increase in the heart rate flexion and extension exercises are increased to per

rest for the heart muscle and circulation is maintained. It is believed that mild deep breathing exercises and moderate flexion and extension exercises of the extremities promote the circulation and lessen the burden on the heart rather than keeping the patient so absolutely quiet that the heart of necessity must do most of the work.

Nursing Care Nursing care must be wisely and intelligently carried out. Comfort rest sleep cleanliness and careful attention to diet and elimination are elementary but essential nursing services. A daily tepid bath with change of linen an attractive diet and intestinal regulation do much to improve the patient's mental attitude toward the disease. As soon as the patient is comfortable he should be permitted to do most of the body hygiene himself. This does not mean that he is permitted out of bed to walk to the bathroom. He is allowed to sit up in bed brush his teeth wash his hands and face and to enjoy his meals when such exercise does not bring on fatigue shortness of breath or increase in the heart rate. The attitude of the nurse should be one of positive approach to health with a good mental attitude rather than a negative approach which constantly inhibits the patient and reminds him of possible danger to his heart.

Diet The diet should be a highly nutritious one. It should be so planned that the patient's nutrition will be well maintained

means permission to sit up with a backrest and to feed oneself. Quiet surroundings in the early stage are imperative so that sleep

vitamins. This diet is best obtained by giving eggs meat fruit and green vegetables. Milk

in moderate quantities should be provided. Excess of sugars, starch, and sweet desserts should be avoided. In the early stages of the illness, when the patient is running a high fever and is restless and uncomfortable, a liquid to a soft diet should be given, that will, however, maintain the caloric content. The average child should receive a caloric content of 2500 to 3000 calories a day, while the young adult should receive at least 3500 calories daily. The form of the diet is entirely dependent on the patient's condition and the stage of activity of the disease.

Drugs. There is no specific drug therapy in the treatment of rheumatic fever. Various drugs have been used, such as aminopyrine, colchicine, cinchona derivatives, calcium benzyl succinate, and many forms of the salicylates, as well as the newer drugs, such as the sulfonamides and penicillin. All drugs have been disappointing in that they fail to attain the goal of the physician, that is, to prevent crippling heart disease. The salicylates are the only drugs which have survived the test of time. Most clinicians agree that the salicylates have an analgesic and antipyretic action. Coburn believed that the early administration of massive doses of the salicylates would prevent crippling heart disease. This work has not been confirmed. It is believed that the salicylates are helpful in the exudative phase of the disease. Their sphere of greatest influence is in their action as a blocking agent, but once the disease is well established, they only modify the inflammatory process. Fever is lowered, painful joints are relieved more rapidly with the use of the salicylates, pain is alleviated, and transudates into the serous cavities are more quickly absorbed during their use. However, they have no effect on terminating the disease process, and no proved effect in preventing heart damage. Furthermore, the salicylates have less and less analgesic and antipyretic value in the second and third cycles of the

permitted activity more readily than if the drug were not administered. Salicylates do not prevent recrudescence of the disease, as seen in the polycyclic type of rheumatic fever. The salicylates should be given in large dosage. The best form of the salicylate

is the acetylsalicylic acid salt, or plain aspirin. The dosage is 1 grain per pound per day, that is, the 30 lb. child would receive 30 grains per day, a man weighing 150 lb. would receive 150 grains per day in equal divided doses administered every 3 hours. It is not necessary to give the salicylate intravenously. Coburn has advocated an intravenous solution of 1000 cc. of a 1 per cent sodium salicylate over a period of 10 hours to maintain a satisfactory blood level of 25 to 35 mg. per 100 cc. of blood. The dosage as mentioned above when given orally will maintain this satisfactory blood level without difficulty. Therefore, the salicylates should be given by mouth in the form of aspirin every 3 hours around the clock. Aspirin is readily absorbed from the stomach. It appears in the blood in 15 minutes and reaches its highest level in approximately 3 hours. It is rapidly eliminated and the blood level begins to fall about the third hour period. Therefore, if the dosage is given every 3 hours, a constant blood level of 25 to 35 mg. per 100 cc. can readily be maintained. It is not necessary to administer sodium bicarbonate with the salicylates. Gastric irritation can be prevented if food is given with each dose of the salicylate. Salicylism can easily be prevented if a large amount of fluid is given with each dose of the salicylate. It is requisite that at least 3000 cc. of fluid be given daily to each patient who is on salicylate therapy. In our experience, only those patients who were not taking an adequate amount of fluid developed salicylism. Salicylism appears whenever the blood level climbs to 50 mg. per 100 cc., or beyond this level. Salicylism, characterized by burning of the eyes, headache, nausea, sweating, drowsiness, and hyperpnea, can be relieved promptly by the administration of large quantities of fluid orally, often without withdrawal of the drug. If the blood level is under 25 mg. per 100 cc., it is easily deduced that the patient is not receiving a calculated dose of 1 grain per pound per day. Since it is impossible to state when a patient with carditis will go either into right or left sided heart failure, it is unwise to give the patient sodium bicarbonate along with the salicylates. Pulmonary edema and passive congestion of the liver are difficult to control if the patient has received large amounts of sodium in the form of sodium salicylate or

sodium bicarbonate Salicylates by rectum are ineffective since doubling the oral dosage raises the blood level to only 7 mg or less Acetylsalicylic acid orally in dosages of 1 grain per pound of body weight given in divided doses at 3 hour intervals with at least 3000 cc of fluid will maintain a satisfactory blood salicylate level of 25 to 50 mg For example a patient weighing 120 pounds should be given 120 grains of aspirin in 15 grain doses every 3 hours around the clock with 400 cc of water with each dose

Hench and his associates reported the effect of 17 hydroxy 11 dihydrocorticosterone (cortisone or compound E) on the acute phase of rheumatic fever stating that in 3 cases there was a rapid disappearance not only of the fever tachycardia and poly arthritis but also of the elevated sedimentation rates and abnormalities of the electrocardiogram The rationale for the administration of the compound E is based on the exhausted state of the adrenal cortex as shown by Selye The author has employed adrenal corticotrophic hormone (ACTH) in an exceedingly acute fulminating rheumatic arthritis with excellent laboratory evidence of improvement in adrenal cortical function and simultaneous drop in the fever tachycardia gallop rhythm leukocyte count and sedimentation rate It has not been shown yet that the primary improvement in the rheumatic activity will be permanent nor has it been proved that their use will not be followed by other manifestations of endocrine dysfunction It is too early to be enthusiastic about this type of treatment but the outlook is hopeful

When cortisone (compound E) or ACTH is being administered the patient must be hospitalized and careful observations of the metabolic status carried out Blood sodium and not

may be tried With cortisone 50 to 100 mg daily is an average dose

Oxygen Oxygen is of great value in the treatment of rheumatic fever rheumatic pneumonitis and congestive heart failure The restlessness cyanosis tachycardia and dyspnea are relieved by the administration of oxygen Oxygen should be given early and as long as the patient requires its help It is best administered by the nasal tube method passing approximately 4 liters of oxygen per minute through a humidifier and into the nasopharynx By this method the coldness of the oxygen tent is avoided and the patient is less annoyed by feeding and nursing care

th
th
administered unless there are signs of congestive heart failure Shortness of breath may be due to pneumonitis or to left sided failure Where there are shortness of breath and evidence of both right and left sided failure digitalis should be given a trial Digitalis glycoside the drug of choice in full dosage should be given over a period of 24 hours and then maintained until the effects are noted If digitoxin is used 0.1 mg per 10 pounds of body weight should be administered in three or four divided doses for the first day For example a boy weighing 120 lbs should receive 1.2 mg of digitoxin in 0.4 mg dosage every 4 hours for three doses Ife then should be continued on 0.1 mg daily

Frequently it is found that digitalis does not improve the heart failure and in the writer's experience it is then best to withdraw the drug entirely Premature beats paroxysmal auricular tachycardia and paroxysmal auricular fibrillation are rare in primary attacks of rheumatic fever They occur frequently where there is serious heart damage that is in second or third recurrences of rheumatic fever

Quinidine Quinidine is not helpful in controlling the attacks in the primary stages of rheumatic fever but may be useful where there is evidence of auricular enlargement as in mitral stenosis Rest oxygen and the avoidance of nicotine are of distinct value in preventing the arrhythmias during the acute carditis of rheumatic fever Quinidine

causes fluid retention and is a danger signal If ACTH is being used frequent eosinophil counts may act as a guide to dosage The specific dose of each drug will vary with the individual patient and depends on the response to treatment Both preparations are administered intramuscularly in divided doses If ACTH is used 60 to 100 mg daily

and related drugs are disappointing in their usefulness

Diuretics Diuretics are used when there is evidence of congestive heart failure. In acute carditis the diuretics are of greater value than any other drug when congestive failure appears. Especially is this true when right sided failure is primary. Right sided failure is frequently primary owing to the associated rheumatic pneumonitis. The diuretic of choice is a xanthine derivative by mouth or salyrgan, mercupurin or mercuhydrin given intravenously or intramuscularly. The preferable method is 1 cc of mercurhydrin intramuscularly every day to insure an output of two thirds of the intake. Mercurial diuretics should not be used if there is evidence of acute glomerular nephritis.

Sulfonamides The sulfa drugs have not proved useful in the treatment of rheumatic fever. The drugs have been used in the treatment of rheumatic fever because of the apparent relationship between the streptococcal throat infections and the active rheumatic state. Since the use of the sulfa drugs is inclined to increase the tendency to develop the collagenous degeneration of the arterioles, it is wise not to use sulfa when rheumatic fever is established. The use of sulfadiazine in 0.5 to 1 gm dosage daily in the quiescent period to prevent recurrent attacks of sore throat may prove wise. However much study should be done on this subject and if there is any question of rheumatic activity the prophylactic use of the drug should be withheld.

Penicillin Penicillin is not beneficial in the treatment of rheumatic fever. It is definitely harmful when continued over a long period of time. Penicillin should be used to clear up the streptococcal sore throat and the carrier state but should not be continued over a period of weeks and months. As soon as the throat has been cleared of the invading streptococcal organism the penicillin should be withdrawn. Intercurrent streptococcal infections of the nose and throat should be treated with penicillin orally or parenterally in dosage of 600,000 units daily.

Vitamins If the rheumatic fever patient is consuming an adequate caloric diet high in proteins it is not necessary to add sup-

plementary vitamins. However, if he is seriously ill and his dietary intake is deficient, vitamins should be added. Vitamin C has been disappointing in that it has not caused a more rapid convalescence. It does tend to help level the temperature curve and the sedimentation rate. Vitamin P, hesperidin, rutin, vitamin K, and calcium in large doses

add a therapeutic dose of the vitamins when the dietary intake is unsatisfactory.

Iron Ferrous sulfate in dosage of 3 to 6 grams three times a day is useful in correcting anemia secondary to the active rheumatic state.

Fever Therapy Fever therapy has not been of value in terminating the active rheumatic state. Chorea clears up rapidly with fever therapy either through the use of typhoid vaccine intravenously or through the use of the Kettering hypertherm. However, if the heart disease and other manifestations of the rheumatic state continue, it is doubtful if fever therapy does more than give temporary relief from the nervous manifestations resulting from the involvement of the central nervous system.

Roentgen Therapy Treatment through the myocardium in the treatment of the active phase of carditis or rheumatic fever has not proved of value in the hands of the author. Levy and Golden from 1926 to 1935 were able to show that roentgen therapy was of value in terminating the active carditis.

Foci of Infection The removal of foci of infection is not attempted in the active phase of the disease. Tonsillectomy during the active phase of the disease resulted in a recrudescence of the rheumatic state in all cases in a series studied by the author. Tonsillectomy was best carried out when the active stage had terminated at least 3 to 4 months previously. The treatment of focal infection in the nasopharynx and tonsils by roentgen or radium therapy has been useful especially where the tonsils are obstructive because of their large size. Dental surgery should be postponed until all signs of rheumatic activity have subsided for at least 3 to 4 months. Blood plasma sera and vaccines have not been helpful in the

treatment of the active phase of rheumatic fever

Climatotherapy Exposure of the rheumatic fever patient to a warm dry climate and regulated heliotherapy is of some general benefit. The virulence of the hemolytic streptococci may be less in a warm dry climate and the fulminating type of rheumatic fever is much less in such an environment. However the incidence of heart disease resulting from rheumatic fever is not much more diminished in the warm dry climate than it is in the climate of the temperate zone. In general it is believed that recrudescence and reactivation of the disease are decreased in a warm dry climate and that heliotherapy is of general health promoting value. However exposure to sun shine must be gradual and well regulated as sunburn can reactivate the rheumatic state as promptly as a streptococcal infection.

Physiotherapy Physiotherapy is definitely harmful in the exudative state of the rheumatic polyarthritides. It is of some value in the older age group when there is residual muscle weakness, pitting and arthralgia, but treatment must be mild and not too vigorous.

Avoidance of Infection Since there is a direct relationship between the degree of carditis and the frequency of reactivation of the rheumatic state, infection must be avoided. At the onset of an upper respiratory infection the rheumatic fever patient, even though he is in the quiescent state, should be put to rest. Isolation should be practiced. Throat cultures should be taken and if the patient has a positive throat culture penicillin should be given orally to clear up the infection and aspirin in large dosage should also be given to act as a blocking agent. With a recurrent upper respiratory infection of a streptococcal nature, care should be taken to find the carrier in the home or in the school and to treat him in order to eliminate such infection. The daily administration of sulfathiazole or sulfadiazine throughout the year will reduce the incidence of streptococcal infection, but the danger of sulfa sensitivity is marked and if sulfa drugs are used prophylactically the patient should be watched carefully for evidence of sulfa sensitivity. The use of penicillin in a prophylactic program is largely inhibited because of the cost. The same is

true for aureomycin at the present time. Since penicillin therapy for the acute hemolytic streptococcal infections of the throat is effective, the occurrence of recrudescence and reactivation can be prevented by the early treatment of the streptococcal sore throat by penicillin.

Convalescence EDUCATIONAL PROGRAM Every child or patient who is convalescing from rheumatic fever should continue with his school work. Most cities and rural districts provide a home school teacher and the patient should be encouraged to follow the school program diligently.

OCCUPATIONAL THERAPY Occupational therapy is of utmost value. In the early phases of the disease when the patient is recovering from the acute illness, diversional

the training for a trade are advisable. Watch making, photography, lathe work, plastics and ceramics all make useful fields for the training of the hands while the child or young adult is at rest in bed. In this manner cardiac invalidism is minimized in the pa-

have an occupation whereby he can become a useful citizen and support himself in the community without throwing a burden on his heart by undue physical activity.

GEORGE C. GRIFFITH

REFERENCES

- Coburn A. F. Salicylate Therapy in Rheumatic Fever. A Rational Technique. *Bull. Johns Hopkins Hosp.* 73:435, 1943.
- 1949
Garcia F. Hyaluronidase Inhibition by Sodium Salicylate in Rheumatic Fever. *Science* 103:680, 1946.
- Hend P. S. et al. Effect of Adrenal Cortical Hormone 17 hydroxy 11 dehydrocorticosterone (Compound E) on Acute Phase of Rheumatic Fever. *Proc. Staff Meet. Mayo Clin.* 24:277, 1949.
- Hirsch H. L. et al. Penicillin Therapy of Scarlet Fever. *JAMA* 133:657, 1947.

- Hoyne A L and Brown R H Penicillin for Scarlet Fever *JAMA* 133 661 1947
- Kyser F A, McCarter J C and Stengle, J Effect of Antihistamine Drugs upon Serum induced Myocarditis in Rabbits *J Lab & Clin Med* 32 379 1947
- Massell B F Dow J W and Jones T D Orally Administered Penicillin in Patients with Rheumatic Fever *JAMA* 138 1030, 1948
- Meads M et al Penicillin in Scarlet Fever *JAMA* 129 785 1945
- Paul J R *The Epidemiology of Rheumatic Fever* New York Metropolitan Life Insurance Company 1943
- Rantz L A Boisvert P J and Spink W W Etiology and Pathogenesis of Rheumatic Fever *Arch Int Med* 76 181 1945
- Rich A R and Gregory J E Experimental Evidence that Lesions with Basic Characteristics of Rheumatic Carditis Can Result from Anaphylactic Hypersensitivity *Bull Johns Hopkins Hosp*, 73 239 1943

ERYSIPELAS

Erysipelas is usually not a primary disease. It tends to follow skin diseases of pyogenic character, such as furuncles, infectious wounds, eczemas, impetigo, chronic otitis media, herpes zoster, and conjunctivitis. Erysipelas tends to occur most frequently in the older age group. Sixty per cent of all cases occur between the ages of 30 and 70. Of 260 cases studied by Charosky, 218 cases occurred on the face, 42 on the legs, with less frequent occurrences on the trunk, arms and genitalia.

The aim of treatment should be prevention. All skin infections particularly suppurative infections, should be cleared up as rapidly as possible. Chronic infections should not be scratched or in any other manner contaminated. Erysipelas which has once become established should be treated promptly. There are two treatments of choice: (1) 25 per cent sulfadiazine ointment applied generously to the infected area at frequent intervals; (2) penicillin by intramuscular injection in a dose of 25 000 to 50 000 units every 3 hours for 48 to 96 hours. 300 000 units given intramuscularly once a day is also a satisfactory form of treatment. A combination of the local application of sulfa ointment and penicillin may be desirable in severe cases. The general treatment consists of rest, a well balanced highly nourishing diet, forcing of fluids up to 3000 cc a day, provided there is no evidence of

heart failure, and good elimination by attention to intestinal regularity. The older methods of treatment, such as painting the edges of the lesion with iodine, magnesium sulfate packs, and ultraviolet or roentgen radiation have been supplanted by the use of the sulfadiazine ointment or the intramuscular use of penicillin.

GEORGE C GRIFFITH

GONORRHEA

Before proceeding with the treatment of gonorrhea, it would be well to establish the diagnosis. All too frequently a nonspecific urethritis is considered to be of gonorrheal origin. A careful history as to exposure and estimation of the incubation period as to the onset of symptoms are of value. The great majority of gonorrheal infections occur within 2 to 9 days after exposure.

The most important diagnostic feature is

which will ferment glucose. The use of complement fixation tests is of some value especially in the metastatic lesions due to gonococci, such as arthritis, where the test is apt to be positive. In acute gonorrhea and in chronic gonorrhea which tends to remain localized at its point of origin, i.e. the urethra, the complement fixation test may be of no value.

Prophylaxis. The prevention of gonorrhea is primarily a public health problem and education of the young adult population is the important task. There has been too much reticence on the part of the doctor and the patient in the discussion of this important disease. Many reputable physicians dislike to care for patients suffering from gonorrhea because of the social nature of the problem. Any doctor who does not know and willingly give advice and treatment to these patients is unmindful of the possible terrible devastation of this disease.

In the armed services the most recent attempt at prophylaxis has been the routine administration of penicillin orally (500 000 units) to all enlisted personnel returning from leave. This has resulted in a significant reduction in the incidence of gonorrhea, but has not completely prevented all cases. It

would seem both possible and practical to give all patients who have been exposed oral penicillin in daily doses of 500,000 units for 3 days, or, one injection of 300,000 units of penicillin intramuscularly

Active Treatment GONOCOCCAL URETHRITIS When the diagnosis has been established, penicillin is the drug of choice. It is important to inspect the urethra and genitalia thoroughly for suspicious lesions, and darkfield examination should be done before any penicillin is given. Penicillin has been known to mask the presence of syphilis in persons having gonorrhea. Therefore, it should be routine for all patients suffering from gonorrhea who are treated with penicillin to have a Kahn test taken at monthly intervals for at least 3 months following the cure of the gonorrhea.

Many opinions exist as to the preparation, dosage, and method of administration of penicillin. At the present time the single dose of 300,000 units of penicillin injected intramuscularly in the gluteal region is most popular. This should be augmented with a sulfa drug, either sulfadiazine or sulfathiazole in 1 gm doses, three times a day. While alkalinization is not essential, bicarbonate of soda in 0.6 gm dosage is best given along with the sulfa.

In most cases so treated, the urethral discharge disappears within the first 24 hours. However, the urine will still contain shreds and pus cells owing to the fact that the ulcerations caused by the gonococci do not heal as fast as the discharge.

At the same time the sulfa and soda are continued. A negative smear of the urethra or stained urine sediment for 3 successive days is a

test of the existence of such acquired resistance. There is no question that some patients are not cured by penicillin and sulfa preparations. This may be due to inaccessible organisms in the prostate, seminal vesicles, or urethral glands by which the patient becomes reinfected when the concentration of the drug (either penicillin or sulfa) disappears. Some of the so-called resistant cases may be pa-

tients who have acquired a nonspecific urethritis along with their gonorrheal infection, or who may have had a pre-existing urethritis or prostatitis.

Provocative tests as criteria for cures are to be condemned, the passage of sounds, and the injection of silver nitrate solutions into a recently infected urethra are of no benefit to the patient.

While the patient is under treatment, it is well for him to avoid alcohol, highly spiced foods, and sexual excitement.

Cure of acute gonorrhea has been effected in from 90 to 100 per cent of all cases with the single injection method of penicillin. Of those not cured by a single injection, the majority are cured by a second injection. Because of the excellent results in the treatment of acute gonorrhea, the incidence of complications has been markedly reduced. It is a well known fact that complications are rare in acute anterior urethritis but fairly common in posterior urethritis.

Posterior urethritis occurs approximately 4 to 6 weeks following the acute anterior urethritis. It is manifested by marked frequency of urination, with tenderness and occasionally some terminal hematuria. There may be constitutional symptoms such as malaise, mild headache and feeling of fullness in the perineum. Fever may be present with leukocytosis.

When posterior urethritis occurs, the patient should be put to bed, and fluids forced to 2500 to 3000 cc daily. An alkaline diuretic, composed of tr. hyoscyamus 10 cc, potassium citrate 10 gm in 3 oz of a suitable vehicle, is prescribed. A teaspoonful three times daily allays the urethral symptoms. If pain is troublesome and the patient is restless, a rectal suppository containing powdered opium, 0.060 gm and extract of belladonna 0.015 gm every 4 to 5 hours gives marked relief.

It is well during the course of posterior urethritis to continue penicillin in doses of 20,000 units every 4 hours intramuscularly. If the sulfa drugs are continued beyond the

unassisted

It is important to cure the posterior ure-

thritus because this is the focus from which the more serious complications develop such as arthritis endocarditis and local extension of the disease as epididymitis orchitis seminal vesiculitis and prostatitis

EPIDIDYMITIS Acute unilateral or bilateral epididymitis does not respond as quickly to penicillin treatment as does the acute gonococcal urethritis. This may be due to the poor drainage of the epididymis. Hence large doses and more prolonged treatment may be required. The testicles should be elevated and constantly immobilized. This is best accomplished by a snug fitting suspensory which has leg straps. The use of cold compresses or a covered ice bag is useful early in epididymitis to minimize swelling after the first 48 hours heat gives relief from pain. Codeine 0.060 gm and aspirin 0.3 gm given in capsule form every 4 to 5 hours are also helpful in relieving pain. Most cases of epididymitis tend to cure themselves spontaneously in 4 to 5 weeks the swelling disappears so that only a small area of scar tissue remains in the globus major of the epididymis. Operation is indicated only when the swelling persists and definite fluctuation is present. In a high percentage of cases of bilateral epididymitis sterility due to aspermia in the ejaculate occurs.

PROSTATITIS Prostatitis due to gonorrhea usually responds to large doses of and prolonged treatment with penicillin. With the patient at rest 20 000 units of penicillin in aqueous solution every 3 hours are given until clinical results are noted. It is not advisable to massage the prostate in order to make a culture until at least one week has elapsed following clinical cure. It is well known that in gonococcal prostatitis other organisms notably staphylococcus and streptococcus intervene and may give rise to a nonspecific chronic prostatitis.

SALPINGITIS Penicillin is effective in salpingitis and pelvic cellulitis before abscess formation intervenes. Treatment should be continued until a smear from the urethra cervix and vagina are negative. Where symptoms persist despite negative smears surgery may be ultimately indicated for removal or drainage of chronic pyosalpinx or hydrosalpinx. Penicillin has been helpful in postoperative management.

VULVOVAGINITIS IN CHILDREN Penicillin is effective here. Doses should be approximately 1000 units per 5 lbs of body weight every 3 hours in very young children. In older children somewhat larger doses approximately 100 000 to 200 000 units daily are given fractionally every 3 hours. Criteria of the cure will be cessation of the signs and symptoms of infection and negative smears for 3 successive days. Segregation of the patient from other children and aseptic precautions should be taken to prevent spread of the infection to others.

OPHTHALMIA NEONATORUM The use of 1 per cent silver nitrate prophylactically in all newborn infants is still a sound principle and should not be abandoned despite an occasional chemical conjunctivitis. If gonorrheal ophthalmia occurs the infant should receive 500 units of penicillin per pound of body weight intramuscularly every 3 hours. In addition penicillin in saline solution containing 1000 to 2500 units per cubic centimeter should be used locally. This should be instilled every 2 to 3 hours during the day. In conjunctivitis with profuse discharge more frequent irrigations are indicated. Treatments are indicated until signs and symptoms subside and smears are constantly negative for 3 successive days.

PROCTITIS While gonorrheal proctitis is uncommon it responds well to penicillin therapy. In severe cases the use of larger doses for a prolonged period of time may be necessary.

ARTHRITIS This is perhaps the most common of metastatic gonococcal complications occurring in about 3 per cent of gonorrheal infections. The knee ankle elbow or wrist is attacked the frequency being in this order. It is usually polyarticular and occurs within 1 to 4 weeks following the primary infection. Sulfathiazole and sulfapyridine are effective in acute gonorrheal arthritis but in chronic cases may not be as effective. Penicillin may be effective in some cases. In acute arthritis 40 000 units every 3 hours usually effect a cure within 3 days. In chronic gonorrheal arthritis the same plan of treatment may be prolonged. Fever therapy is also helpful in chronic arthritis and is combined with penicillin therapy. It is unwise to attempt local treatment of a primary lesion.

such as prostatitis by massage, because of the danger of the exacerbations of the arthritis

Immobilization of the joint and heat help to reduce the pain. Aspiration of the fluid from the joint space is an aid to diagnosis and treatment.

cases

JAMES I FARRELL

CHANCROID INFECTION

Sulfathiazole is effective in this infection. An initial dose of 2 gm is given followed by 1 gm every 4 hours for 7 days. Incision and drainage of fluctuant adenitis are advisable. Dusting of the lesions with sulfanilamide is likewise beneficial. Local treatment should be confined to cleansing moist dressings of 1:8000 potassium permanganate solution. In phimosi a dorsal slit may be necessary for exposure and cleansing of the lesions. It is wise to do several darkfield examinations as syphilis may be a concomitant infection.

JAMES I FARRELL

BRUCELLOSIS

Human brucellosis, commonly known as undulant fever, may be defined as a febrile disease characterized by morning remissions and irregular exacerbations of a multiple of other symptoms and signs. The causative organism may be either *Brucella melitensis*, *Brucella abortus*, or *Brucella suis*. The disease may take the form of a bacteremia or a focal infection.

It is now a well established fact that brucellosis is an animal borne disease and that humans acquire infection from contact with infected animals or through the ingestion of infective animal foods.

The duration of brucellosis is known to vary from 7 days to several years. The variability in its duration often makes it difficult for the physician to interpret the value of specific agents that are used in treatment.

The peculiar behavior of the organism within the host may also account for the poor response of the patient to various therapeutic agents. It has been known since the early studies of Bang that *Brucella* organisms invade and multiply within many types of

fixed tissue cells. Bang's original findings recently have been elaborated on by the work of Castaneda who succeeded in demonstrating large numbers of *Brucella* organisms in many types of tissue cells of mice following experimental inoculation. Large numbers of organisms were seen within macrophages, fibroblasts, endothelial and reticular cells, interstitial cells of the testes, and alveolar cells. It is possible that the intermittent release of bacteria from tissue cells and invasion of new cells is responsible for the wave like form of temperature that characterizes the disease.

The mortality rate in human brucellosis in the United States is still low, but if the organisms continue to increase in virulence as much as they have in recent years, there is the possibility that the disease will take a more severe course in the future and that the death rate will be higher.

A large percentage of cases of the acute form of brucellosis, if recognized within 10 days after the onset and given bed rest and symptomatic treatment will recover from the disease within 6 to 8 weeks without specific treatment. A wide variety of agents has been used for specific treatment. Most of them have been discarded as worthless. *Brucella* bacterins prepared in various forms have been used in the treatment of the disease for more than 30 years. It is the opinion of many physicians who have had considerable experience with brucellosis that bacterins have not proved to be satisfactory therapeutic agents.

Castaneda and Carrillo Cardenas have reported the treatment of 35 cases of *melitensis* brucellosis with a soluble antigen derived from crushed bacterial cells. It is called "MPB". The average duration of symptoms in 35 cases before treatment was 10 months. After treatment the average duration of symptoms was 3.2 months.

For more than 15 years the writer and his associates produced and distributed for the treatment of brucellosis a bacterial filtrate known as "Brucellin". While this agent has served to shorten the duration of symptoms in many acute cases, it is doubtful whether it falls into the category of the kind that is most desired to effect a prompt and speedy cure of the disease.

The reported results from the use of

chemotherapeutic agents such as the sulfonamides in the treatment of human brucellosis are conflicting and confusing. Apparent recovery has been obtained from their use in certain cases but these were an exception rather than the rule.

Recently one of the sulfonamides, sulfadiazine, has received new impetus as a therapeutic agent when administered simultaneously with streptomycin.* Eisele and McCullough have reported complete cures in 2 acute cases with this form of therapy. Spink and associates have obtained complete recoveries in 17 cases with a similar combination of agents. For the average acute case, they recommend the intramuscular injection of 0.5 gm of streptomycin every 6 hours for 2 weeks with an initial oral administration of 4 gm of sulfadiazine and then 1 gm every 4 hours for at least 2 or 3 weeks.

During the past 3 years, the writer has accumulated considerable data from *in vitro* and *in vivo* studies which show that rapid and complete termination of brucellosis in either experimentally infected guinea pigs or naturally acquired cases in human beings can be accomplished by making use of the potentiating property of certain of the sulfonamides on the serum antibody complement system.

It has been found from *in vitro* and *in vivo* studies that normal blood serum or plasma will convert the bacteriostatic action of sulfadiazine to a bactericidal action. The latter action depends on a combination of the drug, normal antibodies, and complement. A bactericidal action was not obtained

in the test tube or in the body of an infected animal by means of the drug in the presence of complement unless normal serum or plasma was added to test tube dilutions of the reagents concerned or was injected intravenously (In *in vivo* studies, complement was furnished by the infected animal).

The curative action of this type of therapy in human brucellosis depends upon maintaining, for a sufficient length of time, a low level (1 to 3 mg per cent) of sulfadiazine in the blood, the presence of sufficient normal antibodies in the donor blood used in the intravenous transfusion, and complement in the blood of the patient. While a marked improvement in the condition of the patient may occur within 48 to 72 hours after the blood transfusion, complete destruction of all *Brucella* organisms present in the tissues of the patient may necessitate the combined presence of the three agents for 7 to 15 days.

The procedure which this laboratory has recommended and which many physicians

have followed is as follows: (1) In children at 4 hour intervals for 24 hours. At the end of the first 24 hour period, give one transfusion of either normal plasma (2 cc. per pound of body weight) or normal whole blood (3 cc per pound of body weight).

The administration of sulfadiazine should be continued at the same dosage and time interval for 7 days after the transfusion. In certain cases, it is advisable to continue the drug for an additional 5 days, giving 7.5 grams twice daily at intervals of 12 hours.

If there is no improvement or only a slight improvement in the condition of the patient within 4 days after the blood transfusion, a second one should be given.

A few physicians, who have used the sulfadiazine-blood transfusion treatment in patients that had been injected previously with *Brucella* antigenic agents (bacterins or culture filtrates) have observed an enhancement of symptoms for 48 to 72 hours after the transfusion. The patients became free from symptoms after the reaction.

Recently Holmes and Hughes reported that they obtained complete cures in 2 cases of *Br. abortus* infection in humans in Eng

* Spink and his co workers feel that aureomycin is as efficient as a combination of sulfadiazine and streptomycin in treating undulant fever. These authors recommend the following dosage of aureomycin in acute cases:

0.1 gm	in four divided doses on the first day
0.6 "	" " " " " " second day
1.6 "	" " " " " " third day
2.0 "	" " " " " " from the fourth to the 10th day

In 2 cases of acute brucellosis, a reported 4 cases of acute brucellosis, combination of aureomycin and streptomycin was administered every 6 hours in a dosage of 750 mg per dose. One gm of dihydrostreptomycin was injected twice daily at 8 A.M. and 8 P.M.—Editor

mycin was administered every 6 hours in a dosage of 750 mg per dose. One gm of dihydrostreptomycin was injected twice daily at 8 A.M. and 8 P.M.—Editor

land through the use of sulfadiazine and blood transfusion therapy

General Treatment The patient should remain in bed during the acute stage of the disease and during specific treatment. After the temperature has returned to normal, complete rest should continue for another 15 days. Noise and excitement should be avoided. As much food should be given as can be assimilated. A warm cleansing bath should be given each morning. Constipation should be corrected with mild laxatives. Headache by the use of an ice cap or cold packs. Nervousness and apprehensiveness may be allayed by bromides or phenobarbital in small doses. Arthritic pains may be reduced by hot applications or radiant heat. Anemia should be corrected with iron. Ascorbic acid in daily doses of 200 to 500 mg is indicated in all forms of brucellosis.

Most patients show a low basal metabolic rate. This should be corrected by the administration of thyroid extract. The adminis-

tion of thyroid extract is recommended in all cases of brucellosis.

Preventive Measures No one who has worked for any length of time with brucellosis would suggest that there is some simple solution to the problem of its prevention. In preventing a disease of this nature in humans one may make use of two well known and workable methods. One involves the detection and slaughter of all infected animals; the other the control of the avenues by which humans become infected from animals. The animal slaughter method of attack should be used wherever practical. The control of the avenues of infection involves the pasteurization of all milk from animals used for human consumption and avoidance of contact with infected animals and raw meat products from such animals.

J FOREST HUDDLESON

REFERENCES

- Bang B. The Etiology of Epizootic Abortion. *J Comp Path & Therap* 10:125 1897
 Castaneda M R. Studies on Pathogenesis of Brucellosis. *Proc Soc Exper Biol & Med* 64:298 1947
 Castaneda M R and Camillo Cardenas C. Treatment of Brucellosis with Brucella Antigens. *Am J Trop Med* 21:185 1941

- Eisele C W and McCullough N H. Combined Streptomycin and Sulfadiazine Treatment in Brucellosis. *JAMA* 135:1053 1947
 Herrell W H and Barber T E. Combined Use of Aureomycin and Dihydrostreptomycin in Treatment of Brucellosis. *Proc Staff Meet Mayo Clin*, 24:135 1949
 Holmes J M and Hughes W. Treatment of Abortus Fever with Sulfonamides and Blood Transfusions. *Brit M J* 2:859 1948
 Huddleson J Forest. The Potentiating Action of Sulfonamides on the Brucella Antibody Complement System. *Am J Vet Research* 11:277 1948
 Huddleson J Forest. *Brucellosis in Man and Animals*. New York: The Commonwealth Fund 1943
 Spink W W et al. Human Brucellosis: Its Specific Treatment with a Combination of Streptomycin and Sulfadiazine. *JAMA* 138:382 1948
 Spink W W et al. Aureomycin Therapy in Human Brucellosis due to *Brucella melitensis*. *JAMA* 138:1145 1948

TULAREMIA

Streptomycin is by universal agreement, the currently preferred agent for the treatment of tularemia (Keefer and Hewitt)*. Its effects are so superior to those of specific antiserum that it has superseded serum ther-

apy administered to desperately ill patients by so many individual physicians has resulted in such a low case fatality rate.

General Therapy Bed rest is enforced during the acute febrile period and during the period of administration of therapy at any stage. The initial diet should be appropriate for the initial clinical status and the nature and quantity of food offered thereafter are largely a matter of appetite, taste and rapidity of convalescence. Sitting up, sitting

*Recently Woodward has indicated that aureomycin may be of more value in the treatment of tularemia than streptomycin. An initial dose of 1 gm followed by 0.5 gm every 4 hours resulted in a normal temperature in 2.5 days after the beginning of treatment. Further observations are necessary before this drug can adequately be evaluated.

out of bed, and ambulatory status are each allowed as soon as return of ability and strength permits. The resumption of work that requires considerable muscular activity is best postponed for at least 2 weeks after fairly good physical competence has been restored. Relapses in tularemia are infrequent but are perhaps more prone to occur following physical exertion soon after spontaneous or induced recoveries (Berson and Harvell). It is worth remembering that there is as yet no evidence that streptomycin has ever killed all of the infecting bacteria in any tularemia patient or in any experimentally infected animal. The available evidence is all to the contrary (Chapman et al.). Hence the crucial event that mediates and conditions recovery is the transfer from a bacteriostatic host dominance over the patient's residual bacteria which is dependent upon the presence of streptomycin to one that is maintained solely by the host's natural defense apparatus. This necessary process of transfer can be accomplished within 36 hours by the nonresistant mouse, but it appears to require a minimum of 4 to 5 days for most treated patients. It is known for both animals and man that this host dominant equilibrium can be upset by overexertion, with consequent endogenous reinfection and clinical relapse. The risk of post therapeutic relapse is greater if therapy is administered for only 1 to 3 days and it is still greater if this too brief treatment period should fall within the first 8 days of the disease. It is difficult to interpret accumulating clinical experience otherwise than that the more severe or prolonged, or both the reaction of the patient to the infection prior to the administration of therapy the less the likelihood of relapse.

Accessory or Special Therapy. Illnesses of great severity are favorably modified so quickly that most of the former accessory or symptomatic measures are no longer needed. With the notable exception of the buboes

visible for a day or two if cyanosis is considerable in the stuporous pneumonic patient who also needs careful watching and preventive measures directed against the development of bed sores. The infrequent patient with enteric infection and intense diarrhea may need parenteral fluids and salts. Moist or dry heat will often ease the pain of large buboes and incision and drainage are necessary for those that suppurate, incision preferably being delayed until liquefaction is well advanced. Ulcerated primary lesions are occasionally secondarily infected with pyogenic bacteria. The mixed infections contribute somewhat to an increased incidence of suppurative lymphadenitis and are therefore of sufficient importance at times to warrant penicillin or other appropriate special therapy, as well as magnesium sulfate or other suitable wet dressings locally. The indications are visible ascending lymphangitis, which is never produced by a pure tularemia infection, continued low grade fever, and buboes that recede much less than is usual under streptomycin therapy. No primary lesion should be incised except to drain abscesses caused by secondary infecting agents.

Streptomycin Therapy. The administration of streptomycin should be started as soon as the diagnosis is made. Deaths from fulminant infections, between the fourth and 10th days of the disease, will not be prevented if precious time is lost in futile efforts to get laboratory confirmation of the diagnosis which must be made solely on epidemiologic and clinical grounds for patients who become desperately ill during the first few days of the disease. Since the earliest possible administration of streptomycin will not prevent the development of specific serum agglutinins, the diagnosis can always be verified after recovery has been achieved. Although the maximal reduction in the duration of the disease and disability is secured by the earliest treatment, streptomycin is highly effective in terminating disability as late as the fourth or fifth month of continuous, febrile disease.

DOSAGE. Although there is still insufficient experience to allow formulation of an average optimal dosage there has appeared no evidence that a total amount of 2 or 3 gm per patient, administered as 0.5 gm per day

removed for physiologic reasons, they are seldom infectious beyond the third day of treatment. Oxygen administration is ad-

for 2 days followed by 0.25 gm per day for 4 days or as 0.5 gm per day for 6 days is not adequate for most patients even those with infections of greater than average severity. There is no evidence yet that dosage in excess of 1 gm per day is necessary requirement or that any total dose greater than 8 gm per patient has actually met a clinical indication that could not have been met adequately with 6 gm or less. Desperately ill patients may need 1 gm or more per day and it may be more effective in the stuporous patient if the first day's quota is administered as a continuous subcutaneous drip rather than by intermittent injections. Frequent observations of changes in the psychic state and the temperature curve form the best clinical guides to quantity and frequency of dosage.

ROUTE AND FREQUENCY OF ADMINISTRATION. All ordinary indications are satisfied by intermittent intramuscular injections of the selected daily dose in three equal portions at 8 hour intervals. Many patients do extremely well if half of the daily intake is injected at 12 hour intervals. It is unnecessary for the great majority of patients to use a 3 or 4 hour injection schedule. The existing meager experience suggests that intrathecal administration is not necessary for satisfactory treatment of tularemia meningitis.

DURATION OF ADMINISTRATION. It is far better to administer moderate doses over a 6 to 8 day period than to give larger amounts for a shorter time. Acute relapses do not occur if the administration period covers a minimum of 5 or 7 days. It is unwise to attempt 3 or 4 day treatments; good remissions may be induced but relapses will occur and it then becomes necessary to do in two sessions what should have been done the first time.

THE HERXHEIMER TYPE OF REACTION. Whenever large pulmonary or serosal exudates are present at the onset of therapy, the analogue of the Herxheimer reaction should be anticipated and if it occurs differentiated from a relapse. This reaction is a consequence of accelerated phagocytosis and solubilization of bacterial bodies with intravascular flooding of antigenic substances owing to the high degree of effectiveness of streptomycin therapy usually appears only in the

sickest patients. It is apt to occur about 1

week and perhaps dizziness or even drowsiness—all of variable intensity and duration depending to some extent on the dosage used and the size of the exudates and usually persisting for 6 to 14 days. It is accompanied by a transitory fall in the agglutinin titer the level rising again spontaneously as the fever subsides. These reactions usually terminate at about the time that resolution of pulmonary exudates can first be detected unlike a relapse they cannot be modified in any way by additional streptomycin therapy. Until now there is no record of the occurrence of a relapse after therapy at any effective dosage level if the duration of treatment was 5 or more days. Several examples of this reaction have been reported (Cohen and Lasser, Foshay).

SUPPURATION OF BUBOES AFTER GENERAL RECOVERY. Although the dosages recommended are sufficient for most patients with tularemia pneumonia the frequency of suppurative lymphadenitis will probably not be reduced by more than 50 per cent. Much more streptomycin is needed to prevent liquefaction of some buboes than is required to prevent death from extensive tularemia pneumonia. A choice apparently lies between higher dosage with a lower frequency of suppuration at an increased risk of impairment of hearing or equilibrium or being satisfied with a 50 per cent reduction in suppuration with minimal risk to the eighth nerve. Since early massive dosage has not prevented all suppuration the latter alternative seems preferable.

TOXIC DRUG REACTIONS. The most cogent reason for administering only enough streptomycin to meet the clinical requirements especially in a disease with a low mortality rate of 74 per cent (Francis), is the well

tration of 12 gm daily for a total of 93 gm about three times the average amount now recommended has resulted in 25 months of partial disability in a former tularemia pa

tient owing to residual vertigo Transitory headache nausea, muscle cramps and general malaise as well as drug fever and tympanitis have occurred following as little as 0.5 gm at rates of 1 gm or less per day Vertigo and deafness are the after effects most to be feared In general the smaller the total dosage, the greater the likelihood that these consequences will be transitory or avoided entirely

EFFECT OF TREATMENT ON IMMUNITY AFTER RECOVERY All evidence presented hitherto indicates that the earliest possible effective treatment does not interfere with the development of the usual high degree of resistance to subsequent external re-exposure that is characteristic of recovered immune cases

STREPTOMYCIN RESISTANCE. In the American clinical experience of more than 20,000 reported cases man to man transfer of tularemia has been so rare and so dependent on gross and easily preventable accidents that one may consider every human infection as a blind alley so far as the future outlook for the infecting bacteria is concerned There is no reason for present concern about the public health consequences of the acquisition of streptomycin resistance by *Bacterium tularensis*

LEE FOSHAY

REFERENCES

- Berson R C and Hurwell A B Streptomycin in Treatment of Tularemia *Am J M Sc* 215 243 1948
- Chapman S S et al Studies on Streptomycin Therapy of Experimental Tularemia in White Mice *J Bact* 51 607 1946
- Cohen R B and Lasser R Primary Tularemia Pneumonia Treated with Streptomycin *JAMA* 131 1126 1946
- Foshay L Diagnosis and Treatment of Tularemia *Postgraduate Med* 4 315 1943
- Foshay L Streptomycin in Treatment of Tularemia *J Indiana M A* 41 207 1948
- Foshay L Comparative Study of Treatment of Tularemia with Immune Serum Hyperimmune Serum and Streptomycin *Am J Med* 1 180 1946
- Francis E Streptomycin in Treatment of Tularemia *Tr A Am Physicians* 60 181 1947
- Hunt J S Pleuropulmonary Tularemia Observations on 12 Cases Treated with Streptomycin *Ann Int Med* 28 263 1947
- Keefer C S, and Hewitt W L Streptomycin Ann Arbor, Mich J W Edwards 1948 pp 165 171

DIPHTHERIA

Preventive Treatment ACTIVE IMMUNIZATION Active immunity is usually conferred by the administration of three doses of fluid or alum precipitated toxoid alone combined with tetanus toxoid, or with tetanus toxoid and pertussis vaccine For the most lasting protection alum precipitated antigen should be injected at monthly or bimonthly intervals at any age after the sixth month of life Should earlier immunization be desirable four monthly doses of the alum precipitated antigen are recommended and the Schick test should be performed 3 or 4 months after the last dose, to determine whether adequate immunity has been conferred For sustained immunity, some authorities recommend a stimulating (reinforcing or booster) dose

better sustained and a stimulating dose is recommended only before entrance into kindergarten or when intimate exposure is likely to have occurred

PROCEDURE AFTER EXPOSURE Whenever a previously immunized child has been exposed to clinical diphtheria a Schick test should be performed and throat and nose cultures should be made If all of these tests are negative nothing further is necessary if the Schick test is positive and the cultures negative, a stimulating dose of toxoid should be administered promptly, if the Schick test and cultures are positive without clinical symptoms, a daily dose of penicillin (300,000 units) should be administered in alternate lateral gluteal areas for several days Only if clinical symptoms of diphtheria arise should antitoxin be used Immunity after recovery from clinical diphtheria is after administration of toxoid usually persists for years, but it is not always permanent Conversely, some individuals are immune without having had either the disease or preventive toxoid

After intimate exposure of a nonimmunized person a Schick test should be performed and throat cultures made promptly If the test is positive and the cultures are negative three doses of diphtheria toxoid should be administered at 3 week intervals and ex

posure should be avoided until active immunity has been established (negative Schick test). If the cultures are positive and the Schick test is negative the patient should be examined daily for clinical evidence of the disease. Nothing should be done except spraying of the throat with penicillin solution (10 000 units per cubic centimeter) 4 to 8 times daily. If cultures remain positive a dose of penicillin (300 000 units) should be administered in alternate lateral gluteal areas for 3 days. Administration of diphtheria antitoxin should be reserved for clinical cases or when the Schick test and cultures remain positive after penicillin.

PASSIVE IMMUNIZATION The decrease in diphtheria morbidity and mortality in recent years and the ability to immunize younger infants adequately with four monthly doses of alum precipitated antigen have made the prenatal injection of expectant mothers by obstetricians an unnecessary procedure.

SCHICK TEST The Schick test is best performed with a 1 cc dry sterile insulin or tuberculin syringe (graduated in 0.1 cc) and a 27 gauge needle. After the inner surface of the left forearm has been cleansed with 70 per cent ethyl alcohol and dried 0.1 cc of the Schick test solution is injected intracutaneously. The best time to make the reading is 72 hours later. In the immune no local reaction is seen; in the nonimmune a local area of hyperemia develops (15 mm or more in diameter). In the immune the diphtheria antitoxin level is at least 0.01 unit per cubic centimeter of serum. A negative test in the newborn is presumed to indicate that adequate antitoxin has been transmitted through the placenta. Both mother and infant show the same kind of reaction—both are either immune or susceptible. In the infant however such immunity is passive i.e. transient and is usually lost after the first few months.

SUPERIORITY OF ALUM PRECIPITATED ANTIGEN The most satisfactory time interval between doses is 1 or 2 months. Many infant welfare clinics and private physicians therefore prefer to administer prophylactic doses of antigens at the time of routine visits.

should be avoided and the vial should be returned promptly to the refrigerator after the required dose has been removed. The superior immunity response after alum precipitated antigen is apparently based on the delay in its elimination from the body whereby prolonged opportunity for the elaboration of specific antibodies occurs. However the earlier in life active immunization is attempted the poorer the immunity response. Therefore infants less than 6 months of age require four monthly doses of slow absorbing antigen.

ADMINISTRATION OF ALUM PRECIPITATED ANTIGENS The injection is best made into the deep subcutaneous tissues of alternate lateral gluteal areas. To reduce the possibility of cyst formation to a minimum it is customary to terminate each dose with 0.1 cc of air which is followed promptly by light massage over the injection site. Subsequent doses should never be administered in sites previously used. Occurrence of a febrile or local reaction is rarely a contraindication for subsequent doses.

COMBINED AND MULTIPLE ANTIGENS Active immunity may be induced by the use of a single combined or multiple antigen. Because diphtheria prevention has long been a well established routine procedure in private practice and in infant welfare clinics tetanus and pertussis immunizations have come to be given with it. At first fluid mixtures of diphtheria and tetanus toxoids were used then alum precipitated. In recent years the alum precipitated and aluminum hydroxide adsorbed multiple antigens of diphtheria and tetanus toxoids and pertussis vaccine have come rapidly into extensive use. The most recent trend is to begin four

exist. In 1943 Lapin wrote "The whole subject of mixed immunization requires a long follow up period to determine which antigen retains antigenicity for a long time." Since then numerous favorable reports have appeared on the use of combined and multiple antigens. In this connection the Council on Pharmacy and Chemistry of the American Medical Association recently issued the following warning "Pending more

knowledge it is suggested that the user be guided by the dosage recommendation given on the manufacturer's product since this represents the dosage accepted by the investigators whose methods have been used in preparing the vaccine. Triple antigen or DTP as alum precipitated diphtheria and tetanus toxoids and pertussis vaccine are now commonly called has rapidly become popular because active immunity can be conferred simultaneously against three diseases and fewer injections are needed. Furthermore slow absorbing (alum precipitated) antigen has been concentrated into a small volume much time is spared for the physician and the parents and the patient's discomfort is minimized.

REACTIONS The reaction after a dose of triple antigen (DTP) is seldom more severe than when each of the antigens is administered singly. A systemic reaction is usually manifested by a transient fever. A local reaction is either an indurated nodule or less frequently a fluctuating cyst which occasionally drains. Should high fever follow a dose the amount of food should be reduced the drinking of water urged and several small doses of aspirin given for a day or two. In a series of over 4000 doses of DTP it was not necessary to subdivide or delay a dose on account of the severity of systemic or local reactions. Contraindications for the administration of antigen are any acute febrile disease, skin infection, prematurity, delay in physical or mental development or any tendency to convulsions. During the 5 years since DTP has been used by the writer no infant or child is known to have developed convulsions after its administration.

STIMULATING (REINFORCING BOOSTER ETC.)
DOSES Basic or primary immunity induced by the administration of diphtheria toxoid singly or combined with tetanus toxoid and pertussis vaccine is usually quantitative. Its duration depends in great measure on the potency and dosage of the antigen, the age of the patient, the time interval between doses and number of doses. A famous immunologist has said "The initial injections constitute the first half of active immunization; secondary stimulation completes it." This so called secondary stimulation may

result from subclinical exposure to the disease or from a single (booster) dose of antigen.

SCHEDULE OF IMMUNIZATIONS

Age	Antigen
6 months*	DTP (alum pptd)
7 months	DTP (alum pptd)
8 months	DTP (alum pptd)
9 to 12 months	Smallpox vaccination
2 to 3 years (before nursery school)	DTP (alum pptd) Booster dose { DTP (alum pptd) Booster dose and small pox revaccination
5 to 6 years (before school)	{ DTP (fluid or alum pptd) booster dose (promptly)
After known exposure of previously immunized	

* If attempted earlier start at 3 or 4 months
DTP (alum pptd) 4 monthly doses

Prophylactic Care of Patient The patient with clinical diphtheria should be isolated promptly whenever possible. He is to be transferred to a contagious disease hospital where he should remain until at least two successive negative nose and throat cultures are reported. If the patient remains at home adequate isolation and precautions are all important. Contacts such as nonimmune children and adults should be quarantined until their cultures are negative. Any member of the household or classroom with a positive culture should be examined every day or two and promptly Schick tested to ascertain immunity or susceptibility. When exposed susceptibles have not been actively immunized and cannot be examined daily a prophylactic dose (5000 units) of antitoxin may be necessary.

Active Treatment SPECIFIC An ample initial dose of diphtheria antitoxin should be administered as early as possible. Only antitoxin that has been kept properly refrigerated and that is not outdated should be used. Antitoxin neutralizes free toxin and inhibits its further elaboration by preventing the growth of bacilli. Damage to the heart and nerves of the critically ill patient can be reduced by prompt intravenous administration.

of at least half of the initial therapeutic dose. Intravenous antitoxin is especially indicated when the larynx is involved. In mild or early cases the intramuscular injection is usually ample. The lateral gluteal area is the site of choice. As a rule at least 100 units per kilogram of body weight (50 units per pound) but never less than 5000 or 10 000 units should be administered. In malignant or advanced cases crystalline penicillin G (300 000 units) may be given intramuscularly at the time of the antitoxin dose and should be repeated once or twice daily until marked improvement has occurred. Penicillin may be given also by mouth (50 000 units buffered tablets) every 3 hours until repeated throat and nasal cultures are negative. If the membrane fails to decrease within 48 to 72 hours the initial dose of antitoxin should be repeated and preferably another brand used. To prevent the occurrence of untoward symptoms such as the Arthus phenomenon antitoxin of any kind should not be reinjected after an interval of 2 weeks.

DESENSITIZATION Before antitoxin is administered 0.05 cc of a 1:20 dilution of antitoxin is injected intracutaneously in the left forearm. If no local or systemic reaction occurs within 15 minutes 0.05 cc of a 1:10 dilution is injected subcutaneously; if no reaction occurs 0.1 cc of undiluted antitoxin is injected subcutaneously; then 0.5 cc is injected intramuscularly; if no reaction results 0.1 cc is injected intravenously and if no reaction occurs the full therapeutic dose is administered. Should a systemic reaction occur at any time 0.5 cc of adrenalin chloride solution (1:1000) should be administered without delay. When sensitivity to horse serum is known to exist or is suspected as in allergic individuals bovine diphtheria antitoxin is recommended but the above outlined desensitization technique should be carried out with it. In serum sensitive patients who are allergic also to bovine antitoxin repeated large intramuscular doses of penicillin are invaluable and curative. If the first dose of penicillin elicits allergic symptoms its use should be curtailed or omitted.

GENERAL CARE Diphtheria patients should be kept flat in bed for at least a week and then activity in bed may be gradually permitted. Toxic and dehydrated patients should be given a daily intravenous drip of 10 per

cent dextrose solution alternating with isotonic amino acid solution. The quantities are governed by the age of the patient, degree of dehydration and height of fever. Excessive amounts of intravenous fluid should be avoided. Proctoclysis may be repeated several times daily if retained. For the older child and adult the bedpan and urinal are imperative. If the bowels are sluggish a daily tepid enema (1 tablespoonful of sodium bicarbonate to 1000 cc of water) is

water)

Drugs When the pulse is of poor quality caffeine (10 mg per kilogram of body weight) may be alternated with adrenalin chloride solution (0.3 cc 1:1000) giving at least two doses of each in 24 hours. If the blood pressure is low a dose of pitressin ($\frac{1}{2}$ ampule) should be administered subcutaneously twice daily. When the cervical glands are enlarged and tender an ice collar may give some relief. Sulfonamides are of value only when a secondary infection is due to a sulfa sensitive pathogen.

Diet At first only fluids should be given by mouth using the drinking tube, dropper or spoon. Water, fruit juices, diluted milk,

improvement is well under way. A 100 mg ascorbic acid tablet should be included in the daily ration; later on vitamins and iron should be added and continued for months.

COMPLICATIONS *Laryngeal Diphtheria* The laryngeal diphtheria patient should be given 20 000 to 30 000 units of antitoxin intravenously as soon as possible and should be kept quietly in bed. Needless excitement and exertion should be avoided. Hospital care is most important at the time when the pseudomembrane sloughs off because respirations are likely to become more labored, and close medical supervision and constant intelligent nursing care are often necessary to save the life. The electric suction apparatus has become an invaluable aid for the removal of mucus and debris from the pharynx, larynx and trachea. Repeated use

of carefully directed suction with the metal catheter has made recourse to intubation and tracheotomy less frequent. Furthermore, cautiously applied suction causes less local injury—as trauma and edema. Moist air (croup tent) and the oxygen tent mask or nasal catheter usually facilitate breathing, decrease cyanosis, anoxia, and toxicity. However, if cyanosis and retraction above and below the sternum increase and repeated and prolonged aspiration with the electric suction apparatus is ineffective, intubation should be resorted to without too much delay. If the tube is coughed up prematurely, as it so often is when too small a tube is used or when the false membrane loosens, immediate replacement of the tube (perhaps the next larger size) may be necessary to prevent fatal suffocation. As a rule 2 or 3 days are long enough for the tube to remain in place; longer than 4 days may cause pressure necrosis which produces scar tissue. In severe cases, especially in infants and young children, nasal gavage feedings are advised for at least 4 or 5 days. The moistened 8 F or 9 F catheter should be inserted only part of the way to the stomach to prevent coughing up of the intubation tube. When relief fails to follow intubation, tracheotomy may be necessary. The lower tracheotomy operation is preferred. Here again the tube should be removed as soon as breathing without it is possible. Before its removal a stopper should be placed into the lumen of the tracheotomy tube for increasing periods of time to determine whether the patient has recovered sufficiently to breathe without the tube without again becoming cyanotic.

Diphtheria Carriers. Cultures from the nose and throat are usually negative within 2 or 3 weeks after the administration of an adequate initial dose of antitoxin. Spraying of the nose and throat with a fresh solution of penicillin (10 000 units per cubic centimeter) six times daily usually speeds up recovery and negative cultures. If the patient is allergic to penicillin, manifested by edema of the tongue or the prompt appearance of a rash after the first dose of the antibiotic, the drug should be discontinued.

Virulence Test. When diphtheria bacilli persist in the cultures without the presence of clinical symptoms, daily intramuscular

dose of crystalline penicillin G (300 000 units) should be administered for several days. If the subsequent cultures remain positive, the Schick test and a guinea pig virulence test should be performed. If the former is negative and the latter proves the bacilli to be nonpathogenic, neither treatment nor isolation is necessary. The persistent presence of virulent bacilli in spite of 100 doses of penicillin may warrant several therapeutic doses of roentgen rays or a tonsillectomy.

LOUIS W. SAUER

REFERENCES

- Schick B. Diphtheria. In: Brennemann McQuarr. *Practice of Pediatrics*. Hagerstown, Md.: W. B. Saunders Company, 1945. Vol. II, Chap. IV.
 Stimson F. M. A Manual of the Common Communicable Diseases. Ed. 4. Philadelphia: Lea Febiger, 1947. Chap. IV.

PERTUSSIS

(Whooping Cough)

Prevention. Because pertussis is more prevalent and causes more deaths during the first two years of life than do the three other preventable contagious diseases—smallpox, diphtheria, and scarlet fever—combined immunization has been attempted as early in life as adequate immunity can be developed. Three doses of fluid pertussis vaccine (total dose 80 000 000 000 bacilli) conferred adequate and prolonged protection to nearly all children when administered after the sixth month of life. When the same dose was injected during the earlier months of life, a appreciable percentage of them failed to develop immunity. Subsequently, Sakakibara, Treuting, Witt, and Nichaman showed that pertussis deaths could be prevented by three monthly doses of alum precipitated pertussis vaccine injected during the first months of life. More recently it was found that three monthly doses of a slow absorbing antigen (such as alum precipitated or aluminum hydroxide adsorbed) pertussis vaccine combined with diphtheria and tetanus toxoids usually conferred good protection against all three of these diseases when begun after the sixth month of life. A higher percentage of infants developed immunity than when fluid antigen—plain mixed or multiple—was

used Immunity tests performed 3 months or more after the final dose showed that 100 per cent had negative Schick tests 96 per cent had tetanus antitoxin levels of 0.1 unit or more per cubic centimeter of serum 83 per cent had positive pertussis agglutinogen skin tests (diameter of induration greater than 10 mm implies immunity) 24 hours later and pertussis complement fixation reactions were 3 or 4 plus in 83 per cent Further more it was found that when primary immunization was attempted before the sixth month of life four monthly doses of alum precipitated triple antigen yielded better protection than did three

TESTS FOR PERTUSSIS IMMUNITY When primary immunization is attempted during the early months of life four monthly doses should be administered and a follow up immunity test (agglutinogen skin test agglutination complement fixation test) should be performed to determine whether adequate immunity has been conferred The skin test is simple to perform reliable and bleeding is unnecessary One tenth cubic centimeter of diluted agglutinogen is injected intracutaneously in the customary site on the left fore arm An area of induration greater than 10 mm in diameter 24 hours later is evidence of immunity to pertussis

ADMINISTRATION OF SLOW ABSORBING ANTIGENS Alternate lateral gluteal regions (starting with the left proximal) are the preferred sites for alum precipitated antigen injections Syringes (1 cc) and needles (25 gauge $\frac{1}{2}$ in) are rinsed only in distilled water and dried before they are sterilized preferably by dry heat (oven at 150° C for one hour) Each deeply administered dose is terminated with 0.1 cc of air The needle remains in place for a few seconds before it is quickly withdrawn It should not deviate from its original course (The infant is held firmly to prevent squirming) Immediately the site is gently massaged with sterile gauze Subsequent doses should not be administered near the site of a previous injection A deep circumscribed nodule may be palpated for a month or longer but the fluctuating or discharging cyst has been almost completely eliminated

REACTIONS Mothers should be forewarned that local and systemic reactions may occur If fever follows a meal should be reduced or

omitted tepid water should be offered repeatedly during the next 12 to 24 hours and several small doses of aspirin should be given in a teaspoon of sugar water During hot weather excessive clothing covers and exposure to the sun should be avoided Regardless of concentration dosage type of antigen time interval between doses or age of infant no adverse systemic reaction other than transient fever is known to have occurred in any infant or child injected by the writer in over 20 years The only local reactions of importance followed alum precipitated antigen A subcutaneous nodule or an occasional alum cyst (mis-called sterile alum abscess) occurred Local reactions have been reduced in frequency and almost completely eliminated by the improved injection technique (see Administration of Slow Absorbing

immunized and after intimate exposure

factors require further study

FAILURE TO CONFER IMMUNITY Before one can conclude that pertussis vaccine has failed to confer immunity it is of importance to exclude *B. paraptussis* infection The differential diagnosis can be made from nasopharyngeal cultures taken early in the disease or later by specific immunologic tests on the serum Failure to confer immunity may be due to one of the following causes

- (1) Impotent antigen may result from
 - (a) use of strains that lacked antigenicity
 - (b) inadequate refrigeration—room temperatures above 10° C (50° F) are deleterious to cultures and vaccine
 - (c) exposure in transit to prolonged high temperature
 - (d) use of outdated vaccine
 - (e) deleterious action of preservative
- (2) Inadequate total dosage For sustained immunity infants less than 6 months of age require four monthly or bimonthly doses of alum precipi

tated antigen also booster doses at 2 and 5 years (see section on Diphtheria Immunization Schedule)

(3) Improperly spaced doses

- (a) too close together (monthly interval is best)
- (b) too far apart (more than 2 months)

(4) Inadequate antibody response

- (a) exposure to pertussis before an adequate antibody level has been attained
- (b) infants—premature, immature, frail or with intercurrent febrile diseases

PASSIVE IMMUNIZATION An intimately exposed nonimmunized child under 2 years of age should be injected promptly with the equivalent of 20 cc of pertussis immune serum—human or 25 cc human hyperimmune globulin. If exposure occurred in the household, the nonimmune infant to whom serum has been administered should be isolated from the patient or with the consent of the local health authorities taken from the premises until the pertussis patient is no longer contagious or until the exposed infant

develop the disease

The prophylactic effect of pertussis immune serum—human (20 cc) or human hyperimmune globulin (25 cc) administered promptly after exposure and the accelerated decline in pertussis morbidity and mortality in recent years have made prenatal immunization of expectant mothers by obstetricians an unnecessary procedure.

Treatment Infants and frail young chil-

drren under 1 year of age who are severely ill should be given 10 cc of hyperimmune globulin (25 cc / 10 cc per cc) daily. McGuinness, Armstrong and Felton recommend that a dose be injected on each of 3 successive days to other young patients a dose every other day until three doses have been given. Patients who fail to show improvement require additional doses. Many infants under one year of age show improvement within a week. Patients over

one year of age may require larger doses especially if improvement fails to occur. A dramatic reduction in the fatality rate has taken place. Critically ill infants should be given intravenously 1 dose of 60 to 100 cc of the serum. Reactions rarely follow. After intramuscular injection local discomfort may continue for a day or two. A slight transient fever occasionally occurs in less than 1 per cent. Patients with a history of allergy may be skin tested with 0.1 cc of serum diluted with its full water content and again diluted 1:10 with sterile distilled water. Skin testing with serum not so diluted may give a positive reaction. A number of clinicians have reported human serum and globulin more effective than refined rabbit serum and far less likely to cause allergic reactions.

GENERAL CARE Most pertussis patients more than a few years old make uneventful recoveries. Fresh, dust-free air and sunshine are beneficial. A week or more in bed decreases the frequency and severity of the attacks of coughing and vomiting.

The food should be easily digestible and rich in vitamins. Excess of fluids, iced drinks and chilled foods should be avoided as priapisms are thus precipitated. For young children puréed food such as vegetables, strained meats, soft-boiled eggs, mashed potatoes, puddings, junket, cereals and bread soaked in warm milk are nutritious and usually well tolerated. Cereals such as rice, farina or cornstarch may be cooked first in half milk and half water, later in undiluted milk. In the case of young infants, suction with a soft rubber bulb syringe may be applied before meals to rid the pharynx of mucus. When vomiting is persistent, five or six small feedings should be tried. Gavage is not used since it provokes coughing and vomiting. When vomiting persists, oral medication should be decreased or entirely omitted for a day or so. When fever and vomiting continue, retention enemas four times daily of tepid water or 5 per cent dextrose solution are of value and may be administered by means of a 14 F lubricated catheter attached to a 2 oz rectal bulb syringe. The tip of the catheter is inserted for a distance of about 3 inches before the tepid contents of the raised bulb are slowly injected. The catheter is pinched off before it

is withdrawn and the knees are kept together for an hour or more to prevent expulsion

Pertussis patients are reluctantly admitted to hospitals during the contagious stage

recovery In hospitals hypodermoclysis of normal saline or 5 per cent dextrose solution may be administered repeatedly Also repeated doses of serum can be given intravenously Isotonic amino acid solution should be used with caution and administered only when indicated Amigen by mouth is safer Infants with severe pertussis require expert nursing care Bactericidal lamps protect against air borne cross infection decrease respiratory complications and destroy exhaled pertussis bacilli Infants and frail young children not infrequently contract enteritis and may have convulsions Convulsions frequently cease soon after the infant has been placed in an oxygen tent The concentration should be maintained at about 50 per cent the temperature should never go below 20° C and the humidity should be kept above 40 per cent

DATOS The age and weight of the patient the severity of the infection and complications determine the kind of drugs and dosage It is hazardous to try to check a severe cough completely by sedation This is especially true in the infant the frail child and any patient who already has a respiratory complication Profuse secretions should be coughed up and out of the bronchi at least several times each day Opium codeine and other sedatives such as the barbiturates should be used with caution preferably only at night to induce rest and sleep and to decrease vomiting The following prescription has been found of benefit

FIG. 1. - 1.1.1

1 to 2 teaspoonfuls or more once or twice at night for severe cough

When the paroxysms are severe and vomiting recurrent sleep and relief are often induced by a retention enema of sulfuric ether (25 per cent) in olive oil (75 per cent) given with a 14 F catheter and small bulb

syringe every 8 hours for a week or longer The usual dose is 1 teaspoonful of the mixture for each year of age It is inflammable There is no danger of necrosis

CHEMOTHERAPY Sulfadiazine is the sulfonamide of choice because it is the most effective and least toxic Although of little value in the treatment of pertussis itself its use may be indicated when secondary infections due to sulfonamide sensitive pathogens occur

ANTIBIOTICS Penicillin is more effective in pertussis and less toxic than are the sulfonamides It is most useful in sulfadiazine resistant or sulfadiazine allergic patients with bronchopneumonia when the pulmonary complication is caused by a pneumococcus streptococcus or staphylococcus If desired both drugs may be given in alternate doses Penicillin may be given by mouth but the intramuscular route is preferred A dose of crystalline penicillin (300 000 units) may be used once or twice in 24 hours To minimize local trauma injections are rotated between the large muscles such as gluteal deltoid and thigh Treatment should be continued for 5 days or more A concentration of 5 mg per cent of free drug in the blood serum is usually adequate

Penicillin is quite effective in respiratory complications if given by mouth in adequate dosage Crystalline penicillin G has the advantage of stability without refrigeration A buffered tablet contains 50 000 or 100 000 units The drug should be given only on an empty stomach at 3 or 4 hour intervals Fasting should be maintained for at least 2 hours after each dose Not infrequently a transient diarrhea subsides within a few days after the drug is stopped When it occurs a boiled milk and a fruit and vegetable free diet should be followed

Streptomycin Streptomycin has been used to advantage when other measures have failed to produce desired results An increasing number of pertussis patients with pneumonia have responded rapidly The preferred method is an intramuscular dose every 12 hours It is important to rotate the site of injection The dosage recommended by the manufacturer should be closely followed Only in exceptional cases should streptomycin be used longer than 10 days In resistant pulmonary complications streptomycin

should be administered by nebulization and inhalation in a concentration of 50 mg per 1 cc of sterile isotonic sodium chloride solution, using about 1 cc every 3 hours. Oral administration is of no value. The most significant untoward effect has been injury to the eighth cranial nerve. It is safer not to exceed 1 gm daily for a maximum of 4 or 5 days. Recently, dihydrostreptomycin has been used without producing most of the untoward reactions from streptomycin.

Chloromycetin Payne et al. have recently reported on 50 cases of pertussis in children under 5 years of age, treated with chloromycetin. This agent was extremely successful in curing the disease. The dosage of the drug varied with the age of the patient, but most patients in Paynes group received 0.25 gm as the initial dose followed by 0.125 gm every 6 to 8 hours. *Aureomycin* is not of value in pertussis.

Complications. Periodic examination of the young patient is advised so that complications can be detected early and treated as they arise. Although most patients can be taken care of in the home, those with complications and infants in congested homes or under circumstances where secondary infection

complications involve the respiratory tract, the gastro intestinal tract, and the central nervous system.

In complications of the respiratory tract, such as bronchopneumonia, especially in infants and frail young children, the oxygen tent or nasal catheter is beneficial, particularly when cyanosis or anoxia occurs. If improvement does not follow repeated doses of human pertussis hyperimmune serum and chemotherapy and a specific type of pneumococcus is isolated from the expectoration or nasopharyngeal swab, administration of the type specific antipneumococcal rabbit serum might accelerate recovery.

Effective treatment when convulsions occur in the home is a hypodermic injection or two of sodium luminal or phenobarbital sodium ($\frac{1}{4}$ to 1 ampule, according to age). If convulsions continue, spinal drainage and continuous use of oxygen for several days are also of benefit.

Gastro intestinal complications, such as enteritis, require careful selection of the proper food. In young infants, during the acute stage, especially if the stools contain

due to a bacterial infection, sulfasulidine in divided doses may be tried for several days to a week. Additions to the diet should be made with caution. After improvement

and fats are most likely to disturb the gastro intestinal upsets, especially diarrhea. The patient's food tolerance should not be overstepped. Ascorbic acid (25 or 50 mg daily) should replace fruit juices until recovery is complete.

LOUIS W SAUER

REFERENCES

- Felton H M Status of Passive Immunization and Treatment in Pertussis *JAMA*, 128 26 1945
 Felton H M and Willard C Y Current Status of Prophylaxis by Hemophilus pertussis Vaccine *JAMA*, 126 294 1944
 Lapin J H Whooping Cough Springfield, Ill. C. C. Thomas 1943
 Payne H N et al Pertussis Treated with Chloromycetin *JAMA*, 141 1298 1949
 Sauer, L. W Whooping Cough Hagerstown Md. W. F. Prior Company, 1946

TYPHOID FEVER

Typhoid fever is an acute infection caused by *Salmonella typhosa* and characterized by a rather typical clinical picture. Management of this infectious disease has improved gradually over the past decade. Prophylactic measures are being used more widely. Recent advances in antibacterial therapy appear to offer better methods of treatment of the active infection.

A detailed description of epidemiologic methods of control of typhoid fever is beyond the scope of this discussion. These methods of control have been described by Anderson and Arnstein and include the proper disposal of sewage, the purification of water, and the prevention of food handling by carriers.

Prophylactic Measures There are certain important prophylactic measures which deal with the care of the individual patient and the protection of susceptible individuals who may come in contact with the patient or with contaminated materials. Infection with *Salmonella typhosa* almost always is due to the ingestion of contaminated food or liquid. The infection is not air borne and therefore good technique should prevent the transmission.

by *Salmonella typhosa* only if the organism reaches his mouth and gastro intestinal tract.

Measures directed toward preventing the transmission of typhoid fever involve the following procedures:

(1) The patient should be isolated and isolation precautions should be maintained if possible until negative results have been obtained on three stool cultures. The windows of the patient's room should be equipped with adequate screens.

(2) The urine and the feces should be disinfected. This can be accomplished by mixing the urine or feces with equal amounts of a 1:1000 solution of bichloride of mercury or a 10 per cent solution of formalin and allowing it to stand an hour or more before discarding it. The fecal material should be broken up before disinfecting. Vomitus and other possibly infected excreta should be rendered harmless in the same manner.

(3) The bedpan or urinal should be sterilized with steam, boiling water or bichloride of mercury solution. Clothing, bedding and utensils should be sterilized by heat or chemicals.

(4) Attendants should scrub their hands with soap and water and immerse them in a 1:1000 solution of mercury bichloride or a 1 per cent solution of cresol after each contact with patients or soiled articles.

(5) All cases of typhoid fever should be reported promptly to the public health authorities so that every effort can be made to determine the source of the infection.

Persons exposed to infection should adhere to the following rules:

(1) Susceptible individuals should avoid contact with the patient or with infected materials as much as possible.

(2) Gowns and rubber gloves give some protection when the individual comes in direct contact with the patient.

(3) The hands should be scrubbed frequently.

(4) Any food or beverage which might be contaminated should be sterilized.

(5) Typhoid vaccine should be administered to all contacts.

Vaccination is a useful adjunct in the prevention of typhoid fever. The protection obtained is only partial but the antibodies induced by the injection of killed typhoid bacilli usually are sufficient to provide a certain degree of immunity. Vaccines usually contain 1,000,000,000 *Salmonella typhosa* organisms and 500,000,000 *Salmonella paratyphi*, A and B, organisms per cubic centimeter of suspension. For an initial vaccination three injections should be administered. The standard method has been to give the injection subcutaneously and the initial dose has been 0.5 cc of the vaccine. Two subsequent injections of 1 cc each are given subcutaneously at intervals of 7 to 10 days. The intracutaneous method of vaccination may be used if desired. The effectiveness of intracutaneous vaccination in protecting the individual seems to be just as great as when the vaccine is injected subcutaneously, and reactions to intracutaneous vaccination are less frequent and less severe. If the intracutaneous method is used the initial dose of vaccine is 0.1 cc, the second injection is 0.15 cc, and the third injection is 0.2 cc. The second and third injections should be given at intervals of 7 days. If an individual is exposed frequently to typhoid fever, he should be revaccinated at least once every 18 months. If he is revaccinated within this period of time a single intracutaneous injection of 0.1 cc of typhoid vaccine is preferable, although a subcutaneous injection of 0.5 cc may be employed.

Local reactions consisting of erythema, swelling, tenderness, and aching often occur at the site of injection, particularly after subcutaneous injections. Systemic reactions consisting of malaise, fever and aching occasionally occur.

Acute Typhoid Fever ANTIBACTERIAL THERAPY Considerable optimism regarding the effectiveness of chloramphenicol (chloromycetin) in the treatment of acute typhoid

fever seems justified at this time. The initial report by Woodward and co workers was encouraging. Further studies have tended to confirm the original observations. The optimal dosage of chloramphenicol still has not been established definitely. Our present program of treatment is to give 50 mg of the drug per kilogram of body weight orally as an initial dose. This initial dose usually is administered in divided amounts at hourly intervals over a period of 2 or 3 hours. Subsequently a dose of 50 to 100 mg of chloramphenicol per kilogram of body weight is administered by mouth daily in divided doses. For an adult the average dose is 3 to 4 gm as an initial dose and 0.5 gm every 3 or 4 hours thereafter. The administration of the drug should be continued until the temperature has remained normal for 7 to 10 days. Nausea and vomiting occasionally occur and may necessitate reducing the dose. Other toxic reactions have not been noted. The response to treatment with chloramphenicol usually is satisfactory. The general condition of the patient improves, the fever gradually subsides, and the results of cultures of the blood become negative. In some patients the gastrointestinal tract may continue to harbor *Salmonella typhosa* as evidenced by persistently positive results on culture of the stool but no symptoms are caused by this.

In order to avoid the possibility of relapse McDermott has treated his patients with a prolonged course of therapy. He gives the patient 6 gm of chloramphenicol daily during the first 3 days or until complete defervescence has occurred, followed by approximately 1.5 gm daily for a total period of 28 to 30 days. This may prove to be a preferable method of therapy if relapses are entirely eliminated.

Treatment of acute typhoid fever with aureomycin, streptomycin, penicillin, and the sulfonamide drugs has been disappointing. However, it is quite possible that in the future a combination of chloramphenicol and one or more of these other antibacterial agents may be the therapy of choice.

If one is located in a community where bacteriophage can be made available, use of this agent can be considered for the patient who does not respond to other forms of therapy. In most instances, however, the

administration of bacteriophage is not practical and the clinical results have been inconclusive.

GENERAL MEASURES. The patient should be hospitalized if possible so that adequate facilities for treatment and for the handling of complications may be readily available. Precautions to prevent spread of the infection as outlined under Prophylactic Measures should be instituted. The patient must rest in bed. Sleep and rest should not be disturbed except when absolutely necessary. The use of sedatives may be indicated in order to insure rest, especially if the patient is delirious. Proper nursing care is important. The bedclothes should be kept clean and dry. The patient should receive a daily sponge bath with soap and warm water. The teeth and mouth should be kept clean. Oil or cream should be applied to the lips to prevent cracking.

It is desirable for the patient to have a bowel movement at least once every other day. Inasmuch as many of these patients are constipated, the use of small enemas with plain water may be indicated. Mineral oil given by mouth may be helpful. Cathartics are contraindicated.

Diarrhea occurs in only a small percentage of patients but at times may be a serious problem. The diarrhea often can be controlled by altering the diet so that it contains only bland foods. Bismuth subcarbonate in a dose of 15 grains (1 gm) every 2 or 3 hours may be helpful. Opium derivatives should be avoided if possible. However, camphorated tincture of opium (paregoric) in doses of 4 cc (1 dram) can be used if other methods fail. The use of this drug is not without risk for it may delay recognition of a perforation.

At least a slight amount of abdominal distention occurs in most patients. However, an attempt should be made to prevent the development of any significant amount for distention can increase the strain on the respiratory and circulatory systems. Distention usually can be avoided by providing a proper diet and using measures to prevent constipation such as enemas or mineral oil by mouth. When distention is present, hot stupes may be applied to the abdomen. An enema, a rectal tube, or gastric suction may be of value.

DIET As in any infectious disease, an adequate diet is essential. In the past the diet of a patient suffering from typhoid fever was rigidly restricted. Most clinicians now feel that the patient should be allowed to eat a diet of his own choosing providing the foods selected are easily digestible, nonirritating and contain an adequate amount of calories, proteins, vitamins and minerals. The difficulty usually is in getting the patient to take nourishment. Patience, tact, and regard for the patient's taste in food are often necessary, if he is to secure an adequate diet. Small frequent feedings are preferable to large feedings. If the patient is toxic or delirious a fluid diet may be all that can be administered. Carbonated beverages (not iced), broth, fruit juices or cereal beverages may be tolerated. The carbohydrate intake can be increased by adding lactose to lemonade.

Supplemental intravenous administration of a solution containing 5 per cent glucose and physiologic saline solution or a solution containing 10 per cent glucose in distilled water usually is necessary in the seriously ill patient. If the patient is not able to take an adequate diet over a prolonged period, or if marked anemia is present, whole blood should be given by transfusion. Small transfusions of 150 to 250 cc of blood every 3 or 4 days are more effective than single transfusions of 500 cc.

As soon as possible soft bland foods should be added to the diet. The following foods may be tried: white bread or toast, well cooked and strained cereals, puddings with out fruit or nuts, butter and cream, tender meat, fish, or fowl, potatoes, macaroni, and refined rice jelly, sugar, and plum candy. Other foods may be added as soon as the patient can tolerate them, although foods known to be irritating to the bowel should be avoided. If diarrhea or distention is present, it may be necessary to reduce the amount of carbohydrates ingested.

Management of the Convalescent Period. The patient should be managed carefully during this period, for relapses occur in a significant percentage of cases. Rest in bed should be continued for at least a week after the patient has become afebrile. Changes in the diet should be made cau-

tiously and the effect of these changes should be observed carefully.

Treatment of Complications. **CIRCULATORY COLLAPSE.** This complication is probably the most important cause of death in typhoid fever. Myocarditis and capillary dilatation often occur during the course of typhoid fever. When these conditions become marked shock ensues. Unfortunately, we have no satisfactory treatment for the shock which occurs in infectious diseases. The cautious intravenous administration of whole blood or fluids may be helpful. Oxygen should be administered, preferably by a Boothby Lovelace Bulbular mask, although an oxygen tent can be used in certain instances. Digitalis is of no avail unless there is actual cardiac decompensation. The patient should be kept warm and inactive.

INTESTINAL HEMORRHAGE. The patient with typhoid fever always should be watched carefully for the development of this complication. If bloody stools are noted, or if there is a sudden drop in temperature accompanied by a rising pulse rate, food should be withheld. Sodium phenobarbital in a dose of 2 grains (0.13 gm) given hypodermically every 4 to 6 hours may produce sufficient sedation. In certain instances morphine sulfate will be required, but it should be used cautiously. In order to avoid the exertion of getting onto a bedpan stools should be passed on an absorbent pad. If the blood pressure falls, or if the bleeding has been profuse, transfusions of whole blood are indicated. The blood should be administered slowly in order to diminish any danger of dislodging the clot. The intravenous administration of some suitable preparation of vitamin K may be helpful. It is always difficult to know when bleeding has ceased. However, if the blood pressure and pulse remain relatively normal for 24 hours, and if there is a cessation of frequent bloody stools, it is usually safe to assume that significant bleeding has ceased. Then small feedings of bland foods can be resumed.

THROMBOPHLEBITIS. The affected extremity should be elevated and warm packs applied. If the prothrombin time is not elevated, the carefully controlled administration of dicumarol seems indicated in order to reduce the danger of a fatal pulmonary

embolus Anticoagulant therapy possibly may increase the risk of hemorrhage. However, hemorrhage on this basis usually can be controlled. Ligation of the femoral vein may be performed if such a procedure appears indicated. However, it is only rarely that such a procedure is advisable.

OTHER COMPLICATIONS Intestinal perforation is a surgical problem and should be treated as an emergency. Acute cholecystitis usually responds to symptomatic measures although surgical treatment may be necessary in certain instances. Osteomyelitis usually will require surgical intervention.

Treatment of Typhoid Carriers The problem of eradicating *Salmonella typhosa* from the stools and urine of patients who continue to harbor the organisms still has not been solved satisfactorily. When the organisms are present in the bile, cholecystectomy should be considered. However, this procedure does not eliminate the organisms from the bowel or from the bile in all cases. Chloramphenicol in doses of 0.5 gm every 3 hours for 2 weeks can be tried, but this drug may not be effective in eliminating *Salmonella typhosa* from the biliary or intestinal tract. Sulfasuxidine, sulfaguanidine, and streptomycin have been reported as curing an occasional patient, but in most instances these drugs are ineffective. All typhoid carriers should be instructed in the methods of disinfecting excreta. They should not be permitted to handle food. Every carrier should be reported to the local department of public health.

DONALD R. NICHOLS

REFERENCES

- Anderson G W and Arnstein M G. *Communicable Disease Control*. Ed 2. New York: The Macmillan Company, 1948.
 McDermott Walsh: Personal Communication.
 Woodward T E et al. Preliminary Report on the Beneficial Effect of Chloromycetin in the Treatment of Typhoid Fever. *Ann Int Med* 29:131, 1948.

SALMONELLOSIS

Bacteria classified as *Salmonella* are capable of producing varying types of clinical infection. On the basis of clinical manifestations these infections due to *Salmonella* may be divided into three main types: (1) *Sal-*

monella fever (enteric fever, paratyphoid fever), (2) *Salmonella enteritis*, and (3) a septicemic type with localization of infection almost anywhere in the body. From a bacteriologic standpoint every *Salmonella* strain is potentially capable of producing any of these clinical types. However, there is a tendency for certain specific strains to produce certain specific clinical manifestations. Treatment of necessity must include antibacterial therapy directed toward the particular strain of *Salmonella* and supplementary measures directed toward the particular clinical type. Typhoid fever is

as typhoid fever has a rather specific clinical course and therefore has been discussed separately from the other forms of salmonellosis.

Anderson and Arnstein describe epidemiologic methods of control of *Salmonella* infections and the proper disposal of sewage, purification of water supplies, and the prevention of food handling by carriers. Most *Salmonella* infections can be transmitted by animals as well as by man. Therefore, control measures include the inspection of animals slaughtered for meat and the supervision of other foods obtained from animal sources.

The prophylactic measures which deal with the care of the individual patient and the susceptible individuals who are in contact with him are the same as those employed against typhoid fever. A certain amount of protection against infections caused by *Salmonella paratyphi A* and *paratyphi B* usually can be obtained by vaccination with the usual typhoid paratyphoid vaccines. The method of vaccination is the same as that outlined for typhoid fever.

Treatment of *Salmonella* Fever (Paratyphoid Fever, Enteric Fever) Although

notably when positive cultures of the blood or stool are obtained.

ANTIBACTERIAL THERAPY Judging from the results obtained in the treatment of typhoid fever, it appears that chloramphenicol (chloromycetin) probably will also be effective in the treatment of some other forms of *Salmonella* fever. Of course, further extensive

investigations will be necessary before a final evaluation of this type of therapy can be made. An initial oral dose of 50 mg of chloramphenicol per kilogram of body weight appears indicated. This initial dose usually should be administered in divided amounts at hourly intervals over a period of 2 or 3 hours. Subsequently a total of 50 to 100 mg of chloramphenicol per kilogram of body weight is administered by mouth daily in divided doses. For an adult the average dose is 3 to 4 gm as an initial dose and 0.5 gm every 3 or 4 hours thereafter. Nausea and vomiting occasionally occur with this dosage and may necessitate reducing the dose. Other toxic reactions have not been noted.

No evidence has been presented yet to indicate that aureomycin will be of much value in *Salmonella* fever. Symptoms at times appear to be relieved when this drug is administered but cultures remain positive. The use of streptomycin in the treatment of *Salmonella* fever also has been disappointing. Again a symptomatic response sometimes is obtained but cultures remain positive. The sulfonamides appear to be of little if any value.

GENERAL MEASURES AND DIET The general measures and diet outlined under Treatment of Typhoid Fever are equally applicable to other forms of *Salmonella* fever.

Treatment of *Salmonella* Enteritis Any strain of *Salmonella* can cause enteritis but *Salmonella typhimurium* and *Salmonella enteritidis* are the predominant organisms found in this type of infection.

ANTIBACTERIAL THERAPY Preliminary studies by Collins, Paine, Wells, and Finland suggest that aureomycin may be of value in certain cases of *Salmonella* enteritis. Aureomycin should be administered to adults in doses of 500 to 750 mg every 6 hours. Aureomycin is quite irritating to the gastro-intestinal tract and may tend to increase the nausea and diarrhea. No reports as to the effectiveness of chloramphenicol (chloromycetin) in *Salmonella* enteritis have

GENERAL MEASURES General measures, including isolation and rest in bed, are necessary in most cases. In the seriously ill patient careful nursing care is important. Bismuth subcarbonate in a dose of 15 grains (1 gm.) every 2 or 3 hours may be helpful in controlling the diarrhea. Camphorated tincture of opium (paregoric) in a dose of 4 cc (1 dram) can be used much more safely than in typhoid fever. If the patient is very toxic oxygen in high concentration should be administered by a face mask.

DIET A bland diet with low residue should be prescribed. If the patient is very toxic a fluid diet may be all that can be administered. Carbonated beverages (not feed) broth or cereal beverages may be tolerated. The supplemental intravenous administration of 5 per cent solution of glucose and physiologic saline solution often is necessary in order to maintain the fluid balance. If the patient is very toxic or if marked anemia is present whole blood should be given by transfusion. As soon as the patient is in a condition to take soft foods the following may be tried: white bread or toast well cooked and strained cereals, puddings without fruit or nuts, butter and cream, tender meat, fish or fowl, potatoes, macaroni, refined rice, jelly, sugar, plain candy. Other foods may be added cautiously as soon as the patient can tolerate them.

Treatment of Localized *Salmonella* Infections This type of infection usually is a complication of *Salmonella* bacteremia. *Salmonella choleraesuis* is the organism most apt to produce these localized lesions.

ANTIBACTERIAL THERAPY No chemotherapy

may be effective; no conclusive studies have been reported as yet.

SURGICAL MEASURES Some of these localized infections due to *Salmonella* are amenable to surgical drainage or excision. The administration of streptomycin by intramuscular injection or chloramphenicol by mouth immediately before and for a few days after surgical treatment may help to prevent further dissemination of the infection.

Treatment of *Salmonella* Carriers Inasmuch as *Salmonella* are frequently excreted in the feces during convalescence from

most varieties of *Salmonella* do not respond to sulfonamides. Streptomycin has not been found of much value.

infections due to this type of organism the persistence of organisms in the stool for several weeks after the acute infection need

should be instructed in methods of disinfecting excreta. Public health authorities should be notified. None of the antibacterial agents have been proved to be effective in eliminating the organism from the stool. Chloramphenicol may be of value in some cases.

DONALD R. NICHOLS

REFERENCES

- Anderson G W and Arnstein M G *Communicable Disease Control* Ed 2 New York: The Macmillan Company 1948
- Collins H S et al Aureomycin—A New Antibiotic: Evaluation of Its Effects in Typhoid Fever, Severe Salmonella Infections and in a Case of Colon Bacillus Bacteremia *Ann Int Med* 9: 1077 1948
- Seligmann E Saphra I and Wassermann M *Salmonella Infections in the U.S.A. Second Series of 2,000 Human Infections Recorded by the New York Salmonella Center* *J Immunol* 54: 69 1948

BACILLARY DYSENTERY

(Shigella Enteritis)

Bacillary dysentery is caused by a group of organisms classified as Shigella. These organisms produce a variable type of clinical picture ranging from a mild diarrhea with out fever to a severe systemic process accompanied by high fever, almost constant diarrhea and circulatory collapse.

Prophylactic Measures. Felsen has shown that the control of bacillary dysentery depends upon the elimination of sources of infection, the prevention of transmission of organisms and the protection of susceptible individuals. In the United States general sanitary measures usually prevent the occurrence of large epidemics. However small groups of cases do occur from time to time and during disaster or war epidemics may occur.

Sources of infection are best controlled by isolating patients and treating known carriers. Susceptible individuals are best protected by insuring the ingestion of only uncontaminated food and water. The use of

prophylactic chemotherapy in certain situations seems advisable.

ISOLATION OF THE PATIENT. The patient should be isolated until cultures of the stool give negative results. The stools should be rendered harmless by mixing with equal amounts of a 1:1000 solution of bichloride of mercury or a 10 per cent solution of formalin. Bedpans, utensils, clothing and bedding should be sterilized by heat or chemicals. Attendants should scrub their hands carefully after coming in contact with patients or contaminated articles.

MANAGEMENT OF PERSONS EXPOSED TO INFECTION. Any food or water which might be contaminated should be sterilized or discarded. The hands should be washed carefully after any contact with patients or infected materials. Prophylaxis with sulfadiazine, streptomycin or one of the newer antibiotics may be indicated in certain instances.

Treatment of Acute Bacillary Dysentery. **GENERAL MEASURES.** In mild cases of bacillary dysentery the disease usually can

supportive measures are important adjuncts to the antibacterial therapy. Strict rest in bed is of importance. Sedatives may be necessary to insure proper rest. Careful nursing care is indicated for the seriously ill patient.

Fluids lost through diarrhea or vomiting must be replaced by appropriate methods in order to avoid the effects of dehydration. Liquids can be taken orally unless the patient is nauseated and vomiting. If the oral intake is inadequate, the intravenous administration of physiologic saline solution or of 5 per cent solution of glucose is indicated. Transfusions of whole blood are of value in the treatment of seriously ill patients especially if there is any hypoproteinemia or anemia.

Control of the diarrhea and relief of pain can be obtained by administering camphorated tincture of opium (paregoric) in doses of 4 cc (1 dram) or powdered opium in doses of 2 grains (0.13 gm) orally every 3 or 4 hours. Bismuth subcarbonate in doses of 15 grains (1 gm) or milk of bismuth in doses of 4 cc (1 dram) may be added if the diarrhea is severe. Hot stupes to the abdomen

may help alleviate the pain. If tenesmus ■

to liquids. If there ■ much vomiting or distention, it may be advisable to withhold liquids and food for ■ short period and rely on parenteral administration of fluids to maintain the fluid balance. As soon as possible a liquid diet should be resumed. Broth, carbonated beverages (not iced), and cereal beverages are usually well tolerated. Sugar may be added in moderate quantities. As soon as the diarrhea has been controlled a bland diet can gradually be started. The following foods may be tried: white bread or toast, well cooked and strained cereals, puddings without fruit or nuts, butter and cream, tender meat, fish or fowl, potatoes, macaroni, and refined rice, jelly, sugar and plain candy. This bland diet should be continued for several days and then a normal diet can be resumed cautiously. In the seriously ill patient vitamins of the B complex should be administered parenterally during the acute phase. If the convalescence is prolonged, the diet should be supplemented by vitamins administered orally.

ANTIBACTERIAL THERAPY In the mild forms of bacillary dysentery the use of chemotherapeutic agents usually is not necessary. However, in all cases except the mild ones some form of chemotherapy ■ indicated.

Sulfonamides Many of the sulfonamide drugs exert a bacteriostatic effect upon bacteria of the genus *Shigella* according to Hardy and Watt. However, not infrequently sulfonamide resistant strains are encountered. Sulfadiazine ■ an effective form of therapy in many severe forms of bacillary dysentery, especially when it ■ given within the first 24 hours of symptoms. Diarrhea and abdominal pain usually cease within a day or two after the onset of treatment with this drug. The temperature becomes normal in about the same period of time. The inflammatory changes in the bowel cease to progress. However, Smith has shown that actual healing of the mucosal lesions does not take place as rapidly as does the symptomatic relief. If the inflammatory process has progressed to the stage of ulceration, healing may not be complete for several

weeks. Therefore, the administration of sulfadiazine early in the course of the disease is important if the inflammatory changes are to be readily controlled.

Administration of sulfadiazine should be started as soon as a tentative diagnosis of bacillary dysentery has been made. An initial dose of 60 grains (4 gm) of this drug is administered by mouth and a dose of 15 grains (1 gm) should be given subsequently every 4 hours. If the patient is dehydrated, intravenous administration of fluids should be started soon after the initial dose of sulfadiazine so that there will be an adequate urinary output. If the patient is not dehydrated, fluids by the oral route alone usually will suffice. However, it is imperative that the patient receive enough fluids to insure a urinary output of about 1500 cc. The administration of sodium bicarbonate in doses at least equal to the doses of sulfadiazine is advisable. The administration of sulfadiazine should be continued for a minimum of 72 hours and for at least 48 hours after the temperature has returned to normal. If the use of the sulfonamide is continued for several days, the cells in the urine and the number of leukocytes in the blood should be watched carefully.

The poorly absorbable sulfonamides, such as succinylsulfathiazole (sulfasuxidine) or sulfaguandine have been shown to be effective in many cases. The results, in general, are not as good as those obtained with sulfadiazine. However, if a situation arises wherein the patient cannot be kept under close observation, the use of succinylsulfathiazole (sulfasuxidine) usually will be the therapy of choice. Succinylsulfathiazole should be given in doses of 75 grains (5 gm) every 6 hours for a minimum of 5 days and preferably, until the results of rectal cultures are negative.

Streptomycin If the patient does not respond well to sulfadiazine, a trial of streptomycin is indicated, for most strains of *Shigella* are sensitive to streptomycin. Pulaski has obtained satisfactory results using a daily dose of ■ gm of streptomycin orally in divided doses.

In certain instances both the oral and intramuscular administration of streptomycin seems indicated. An intramuscular injection of 0.5 gm of streptomycin every 8 hours and

an oral dose of 0.5 gm every 8 hours is a satisfactory schedule for adults. Dihydrostreptomycin may be substituted for streptomycin if desired. The intramuscular use of streptomycin is contraindicated if there is any renal insufficiency, but oral therapy usually can be continued, inasmuch as there is little absorption of streptomycin from the gastrointestinal tract.

Aureomycin. From preliminary laboratory studies it would appear that aureomycin will be an effective agent in the treatment of bacillary dysentery. Further clinical investigation will be necessary before final conclusions can be reached regarding the place of aureomycin in the treatment of this infection. It is quite possible that aureomycin may become the drug of choice in the treatment of bacillary dysentery.

Chloramphenicol (Chloromycetin). In vitro, the *Shigella* organisms are sensitive to chloramphenicol. Therefore use of this drug may prove to be an effective form of therapy. No clinical trials have been reported as yet.

Complications. **ARTHRITIS.** This complica-

are rare. These complications should be treated with vigorous antibacterial therapy. At the present time sulfadiazine given orally or streptomycin given intramuscularly in the doses previously advised appear to be the drugs of choice. In the future aureomycin or chloramphenicol may prove to be a superior therapeutic agent for these serious infections.

DONALD R. NICHOLS

REFERENCES

- Felsen, Joseph. *Bacillary Dysentery, Colitis and Enteritis*. Philadelphia: W. B. Saunders Company, 1945.
 Hardy, A. V. and Watt, J. *Acute Diarrheal Diseases*. J. A. M. A. 124:1173, 1944.
 Pulaski, E. J. *Personal Communication*.
 Smith, L. A. *Shiga Dysentery (Bacillary Dysentery)*. J. A. M. A., 130:18, 1946.

CHOLERA

Prevention. Since cholera is essentially a disease dependent on poverty, overcrowding, and bad hygienic conditions, it can best be prevented by improving the standard of living which includes education, public and personal hygiene, modern sewage disposal, control of vermin, refrigeration and control of food and drink. Cholera has disappeared from many communities as a result of these improvements alone, but it may occur at any time anywhere when conditions favor it. The outbreak in Egypt in 1947 is an example of such an occurrence.

Because man, so far as is known, is the only source of cholera, it could be exterminated if all patients could be strictly isolated and all carriers quarantined. Unfortunately, this cannot be accomplished.

During epidemics or in endemic areas water for domestic use should be efficiently chlorinated, boiled or obtained from sources known to be free from contamination. Food should be handled carefully, refrigerated and protected from insects. Flies and vermin must be controlled by screens, traps, swatters, repellents and insecticides. Most effective are preparations of DDT which can be sprayed into closed spaces or painted on walls and screens of rooms, latrines and garbage racks. Feces from cholera patients or carriers should be disinfected before disposal or buried in deep covered pits. Feces

gm) every 4 hours often will give symptomatic relief.

CHRONIC BACILLARY DYSENTERY. This complication is a form of ulcerative ileocolitis which occasionally follows an attack of severe bacillary dysentery. Streptomycin administered orally in a dose of 1 gm three times daily is often effective in eliminating the infection. Aureomycin in doses of 750 mg every 11 hours may be effective. The sulfonamides, either sulfadiazine or sulfasuxidime, or both are of proved benefit if the organisms are not sulfonamide resistant. Chloramphenicol may prove to be of considerable value, however, clinical studies of the effectiveness of this substance have not been reported as yet. As in acute bacillary dysentery, particular attention should be paid to the diet. The foods previously mentioned under "Treatment of Acute Bacillary Dysentery" will serve as a basic diet, and additions to this diet can be made cautiously. Supplemental use of vitamins may be indicated if the disease has been of long duration.

OTHER COMPLICATIONS. Localized infections, such as endocarditis and meningitis,

in open latrines should be sprayed or dusted with DDT

VACCINE The value of vaccination against cholera is uncertain. Vaccination alone has never controlled an outbreak and vaccinated persons may acquire a false sense of security. To be effective, vaccine must contain antigens similar to those of the strain or strains rampant at the time. Immunity evoked by vaccine does not last more than several weeks or months. If used, vaccination with heat-killed vibrios consists of an initial dose of 0.5 cc followed in 7 to 10 days by 1 cc
ses of there

Important factor is to eat or drink food or beverages which are known to be safe or which have been thoroughly cooked or boiled. Sterilized food and drink may be infected later by flies or by hands soiled with feces. Food may be contaminated by soiled containers or by washing or mixing it with polluted water or ice. Uncooked vegetables and fruits should not be eaten. Uncontaminated water or water sterilized by boiling or by chemicals must be used. Vigilant supervision of the operations of native Asiatic or African servants and cooks and of their health is necessary.

Fatigue and excesses of any kind must be avoided. Patients increase susceptibility to cholera.

Treatment Prompt and vigorous treatment is imperative and management must be regarded as an emergency measure. Treatment begun within a few hours of the onset is most successful. Proper treatment can be given easily to small groups of patients when adequate medical and nursing aid and adequate hospital facilities are available. However, in places where cholera occurs and for the reasons that it occurs, conditions often are primitive. Under such conditions a sudden outbreak with hundreds of patients at once makes the cure of all but a few impossible and accounts for the high mortality rate. Treatment includes the management of the patient and of the epidemic as well.

Patients should be cared for in hospitals

whenever possible where therapy and isolation are managed more easily. During an epidemic or otherwise, patients with mild attacks or those suspected of having cholera should be kept in bed, isolated and observed. Their excreta should be examined carefully for *V. comma*, sterilized or properly buried.

Treatment should be commenced as soon as possible after a history is taken, a physical examination is made, a blood count and urinalysis are done, the pressure and the specific gravity of blood are measured, and smear and culture of the stool are made. All data, including temperature, volume of the stool, vomitus and urine and amounts of fluid ingested and injected, should be recorded in chart form. Even if no vibrios can be seen in smears of the stool, treatment should be started, since cultural studies and identification require several days for completion.

FLUIDS Water containing 1 per cent sodium bicarbonate should be offered in small amounts every 15 minutes if there is no vomiting, but more rapid rehydration and remineralization are urgent in severe attacks. Intravenous injection of isotonic solution of sodium chloride warmed to near body temperature should be given at once at the rate of 60 to 100 cc a minute in amounts of 1000 to 2000 cc depending on the size of the patient and the specific gravity of the blood. About 300 cc. of 2 per cent solution of sodium bicarbonate are added to the first infusion and to subsequent ones if collapse or acidosis is evident. Febrile reactions often occur from solutions prepared under unfavorable conditions, but the urgency of treatment outweighs the dangers therefrom. If veins are inaccessible or cannot be entered, the intramedullary route of injection into the sternum or tibia may be used.

Amazing improvement often occurs rapidly, but in many instances purging and vomiting continue, collapses recur and require repeated injections, sometimes every 3 or 4 hours. Relatively enormous amounts of fluid are needed for cholera. As much as 10,000 cc has been infused continuously within the first few hours and more than 14,000 cc in a 24-hour period. Injections may have to be given over 2 or 3 days.

The specific gravity of the blood must be

measured at the bedside, preferably with

than 1058, more fluid is needed. If actual measurements cannot be made, judgment as to the amounts needed must be guided by the clinical response, blood pressure, pulse rate, consistency of the blood, and output of urine. Care must be taken not to give too much lest overfilling occur, signaled by restlessness, palpitation, substernal oppression, cough, or edema.

Sterile, pyrogen free isotonic solution of sodium chloride (9 gm sodium chloride to 1000 cc water) is the fluid of choice. Some clinicians prefer to add 5 per cent dextrose, but not more than 400 gm of glucose should be given in 24 hours. Thiamine chloride, 1 mg for every 25 gm of dextrose may be

of injecting plasma for the shock like state is controversial.

ROUTINE CARE The management of a cholera patient is otherwise the same as for any severe infection of the gastro intestinal tract. Patients should be strictly isolated. Clothing, bedding, and personal articles should be sterilized by washing with soap and hot water, by boiling, or with chemicals. Alvine discharges and vomitus must be disinfected with 1:1000 solution of mercury bichloride or other germicide before disposal in a sewage system. Otherwise they should be emptied into a deep, covered pit, remote from any water supply or kitchen. Attendants must be taught to observe rigid rules of hygiene. Flies and vermin must be exterminated.

The patient should have a minimum of disturbance. During periods of chill and collapse the body should be covered and warmed to normal temperature with hot water bottles or heated coverings. Water and liquid or semisolid food may be given, if desired by the patient. Restlessness may be treated with barbiturate compounds or with morphine. The latter may be used for the severe pain of muscular cramps. Complications are uncommon but should be anticipated and treated.

Drugs Digitalis or other cardiac and circulatory stimulants are not needed unless heart disease itself is present. Medicaments, such as purgatives, enemas, intestinal antiseptics, constipating agents, opium, specific immune serum, bacteriophage and others are of no proved value and are not recommended.

Penicillin and streptomycin are of no value. Opium differs as to the effectiveness of sulfadiazine. Chu and Huang gave sodium

agreement with my own observations. Sulfaguanidine, however, was said to have reduced the mortality rate from 75 per cent to 37 per cent in otherwise well treated patients in hospitals, and from 41 per cent to 18 per cent in patients in their homes where supportive treatment was not given. Bhatnagar used 20 to 30 gm of a new sulfonamide formaldehyde compound called "6257" and reported good results in all his patients. If the value of either sulfaguanidine or "6257" is confirmed, mass treatment will be greatly simplified if there is no need for injection of fluid. Further study of these drugs is indicated.

Convalescence Recovery, even without treatment, is often surprisingly rapid but rest in bed should be enforced reasonably for several days. Subsequent fatalities may occur suddenly, some of them perhaps from embolism. Fluid and soft, easily digested foods both preferably warm or hot, may be offered as soon as desired by the patient. Patients should not be released from control until their stool cultures no longer contain *V. comma*.

HOBART A. REIMANN

REFERENCES

- Bhatnagar S S, et al. Chemotherapy of Cholera with a New Sulphonamide Compound (6257), Laboratory Investigations and Field Trials. *Brit M J*, 1:719 1948.
Chu L W and Huang C H. Effect of Sulfadiazine on Cholera. *Am J Trop Med*, 26:821 1948.

Treatment

PLAGUE

Prophylaxis The control of plague like that of cholera is largely a problem of economics and education. With the abolition of poverty and squalor and an improvement of the standard of living the conditions favoring the spread of plague from rodents to man and from man to man by way of the flea or otherwise disappear spontaneously. However, since poverty, ignorance and overcrowding still persist in many areas of the world, plague is an ever-present menace which must be guarded against by other measures.

EXTERMINATION OF THE SOURCE AND VECTOR Rats or other rodents which harbor plague bacilli and their vectors must be exterminated or prevented from coming in contact with people. Concrete foundations or other ratproofing of buildings is desirable but expensive. Ships coming from endemic areas should be fumigated with hydrocyanic acid gas or sulfadiazine and hawser shields provided when docked. Rats may be trapped with snap traps but according to Macchiavello they are effectively controlled by a fluorine raticide called 1080. Technical difficulties often interfere with destruction of rodents and many believe that an attack on the flea vector with the insecticide DDT is of great importance. Persons in endemic or epidemic areas should be dusted with DDT in powdered talc or wear clothing impregnated with it. Repellent agents such as pyrethrum are less reliable.

CHEMOPROPHYLAXIS Daily oral administration of 3 gm. of sulfadiazine apparently was successful in preventing plague in small groups of exposed persons. The method has not been tried in field tests and it is questionable if it is justified or reliable in uncontrolled groups because of the toxicity of the drug.

VACCINE The value of antiplague vaccine is not agreed upon and its use tends to give a false sense of security. Furthermore, there are different serologic varieties of plague bacilli which require a high degree of specificity of the vaccine. Living "attenuated" plague bacilli have been used as vaccine with reported successful results in Africa but the danger inherent in such a practice does not justify its general use. The injection

of antiplague serum to provide passive immunity is not warranted.

QUARANTINE. Quarantine as managed by specially trained public health officers with recognized authority to enforce rules and co-operation on the part of the public is of great importance. The dissemination of instruction and advice paves the way for effective control. Patients and persons in contact with patients should be isolated.

Physicians and attendants dealing with an epidemic should wear clothing impregnated with DDT or insect proof clothing, boots and gloves. Those in contact with pneumonic plague should wear a complete hood or thick mask over the nose and mouth to avoid inhaling bacilli suspended in the air.

Treatment The general management is the same as for any severe infectious disease. Bed rest is imperative. Diet and fluid intake should be adequate. Morphine may be needed for extreme restlessness or painful buboes. Oxygen is helpful when pneumonic is present. The circulatory system requires especial attention but digitalis is not necessary. Buboes should be covered with hot moist compresses and not incised. If tense with pus, aspiration with a hollow needle is advised.

At present, according to numerous reports, sulfadiazine is the drug of choice for specific therapy, but well controlled large scale studies have not been made. Early treatment is most effective. The initial dose of sulfadiazine is 4 gm. followed by 1 gm. every 4 hours. In comatose or uncooperative patients, sodium sulfadiazine may be given intravenously.

Recent reports indicate that *streptomycin* is effective in curing the disease in experimental animals and has been used with success in a few patients in doses of 2 to 4 gm. daily. In one with the pneumonic form contracted in a laboratory, Huang and his associates had good results. The dosage is not established but probably rests between 1 and 3 gm. daily in divided doses given intramuscularly.

Antiplague serum has its advocates but is of little value. It is expensive, its administration is complicated and it often causes a severe reaction and serum disease. Bacteriophage is of no value.

HOBART A. REIMANN

measured at the bedside, preferably with

than 1058 more fluid is needed. If actual measurements cannot be made, judgment as to the amounts needed must be guided by the clinical response: blood pressure, pulse rate, consistency of the blood, and output of urine. Care must be taken not to give too much lest overfilling occur, signaled by restlessness, palpitation, substernal oppression, cough, or edema.

Sterile, pyrogen free isotonic solution of sodium chloride (9 gm sodium chloride to 1000 cc water) is the fluid of choice. Some clinicians prefer to add 5 per cent dextrose, but not more than 400 gm of glucose should be given in 24 hours. Thiamine chloride, 1 mg for every 25 gm of dextrose, may be

of injecting plasma for the shock like state is controversial.

ROUTINE CARE. The management of a cholera patient is otherwise the same as for any severe infection of the gastrointestinal tract. Patients should be strictly isolated. Clothing, bedding and personal articles should be sterilized by washing with soap and hot water, by boiling or with chemicals. Alvine discharges and vomitus must be disinfected with 1:1000 solution of mercury bichloride or other germicide before disposal in a sewage system. Otherwise they should be emptied into a deep, covered pit, remote from any water supply or kitchen. Attendants must be taught to observe rigid rules of hygiene. Flies and vermin must be exterminated.

The patient should have a minimum of disturbance. During periods of chill and collapse the body should be covered and warmed to normal temperature with hot water bottles or heated coverings. Water and liquid or semisolid food may be given if desired by the patient. Restlessness may be treated with barbiturate compounds or with morphine. The latter may be used for the severe pain of muscular cramps. Complications are uncommon but should be anticipated and treated.

Drugs. Digitalis or other cardiac and circulatory stimulants are not needed unless heart disease itself is present. Medicaments such as purgatives, enemas, intestinal antiseptics, constipating agents, opium, specific immune serum, bacteriophage, and others are of no proved value and are not recommended.

Penicillin and streptomycin are of no value. Opinion differs as to the effectiveness of sulfadiazine. Chu and Huang gave sodium

to 37 per cent in otherwise well treated patients in hospitals, and from 41 per cent to 18 per cent in patients in their homes where supportive treatment was not given. Bhatnagar used 20 to 30 gm of a new

or "6257" is confirmed, mass treatment will be greatly simplified if there is no need for injection of fluid. Further study of these drugs is indicated.

Convalescence. Recovery, even without treatment, is often surprisingly rapid, but rest in bed should be enforced reasonably for several days. Subsequent fatalities may occur suddenly, some of them perhaps from embolism. Fluid and soft, easily digested foods both preferably warm or hot, may be offered as soon as desired by the patient. Patients should not be released from control until their stool cultures no longer contain *V. comma*.

HOBART A. REMANN

REFERENCES

- Bhatnagar S, et al. Chemotherapy of Cholera with a New Sulphonamide Compound ("6257"). Laboratory Investigations and Field Trials. *Brit M J*, 1:719 1948.
- Chu L W and Huang C H. Effect of Sulfadiazine on Cholera. *Am J Trop Med* 26:821 1946.
- Paschke C L, et al. Sulfaguanidine in Treatment of Cholera. *Indian M Gaz*. 82:518 1947.
- Remann H A. Cholera in *Oxford Medicine*. New York, Oxford Publishing Company, 1947, Vol 4 p 783.

PLAGUE

Prophylaxis The control of plague like that of cholera is largely a problem of economics and education. With the abolition of poverty and squalor and an improvement of the standard of living the conditions favoring the spread of plague from rodents to man and from man to man by way of the flea or otherwise disappear spontaneously. However, since poverty, ignorance and overcrowding still persist in many areas of the world, plague is an ever present menace which must be guarded against by other measures.

EXTERMINATION OF THE SOURCE AND VECTOR Rats or other rodents which harbor plague bacilli and their vectors must be exterminated or prevented from coming in contact with people. Concrete foundations or other ratproofing of buildings is desirable but expensive. Ships coming from endemic areas should be fumigated with hydrocyanic acid gas or sulfadiazine and hawser shields provided when docked. Rats may be trapped with snap traps but according to Machiavelli they are effectively controlled by a fluorous raticide called "1080". Technical difficulties often interfere with destruction of rodents and many believe that an attack on the flea vector with the insecticide DDT is of great importance. Persons in endemic or epidemic areas should be dusted with DDT in powdered talc or wear clothing impregnated with it. Repellent agents such as pyrethrum are less reliable.

CHEMOPROPHYLAXIS Daily oral administration of 3 gm of sulfadiazine apparently was successful in preventing plague in small groups of exposed persons. The method has not been tried in field tests and it is questionable if it is justified or reliable in uncontrolled groups because of the toxicity of the drug.

VACCINE The value of antiplague vaccine is not agreed upon and its use tends to give a false sense of security. Furthermore, there are different serologic varieties of plague bacilli which require a high degree of specificity of the vaccine. Living "attenuated" plague bacilli have been used as vaccine with reported successful results in Africa, but the danger inherent in such a practice does not justify its general use. The injection

of antiplague serum to provide passive immunity is not warranted.

QUARANTINE Quarantine as managed by specially trained public health officers with recognized authority to enforce rules and co-operation on the part of the public is of great importance. The dissemination of instruction and advice paves the way for effective control. Patients and persons in contact with patients should be isolated.

Physicians and attendants dealing with an epidemic should wear clothing impregnated with DDT or insect proof clothing, boots and gloves. Those in contact with pneumonic plague should wear a complete hood or thick mask over the nose and mouth to avoid inhaling bacilli suspended in the air.

Treatment The general management is the same as for any severe infectious disease. Bed rest is imperative. Diet and fluid intake should be adequate. Morphine may be needed for extreme restlessness or painful buboes. Oxygen is helpful when pneumonia is present. The circulatory system requires especial attention but digitalis is not necessary. Buboes should be covered with hot moist compresses and not incised. If tense with pus, aspiration with a hollow needle is advised.

At present, according to numerous reports, sulfadiazine is the drug of choice for specific therapy, but well controlled large scale studies have not been made. Early treatment is most effective. The initial dose of sulfadiazine is 4 gm followed by 1 gm every 4 hours. In comatose or unconscious patients, sodium sulfadiazine may be given intravenously.

Recent reports indicate that streptomycin is effective in curing the disease in experimental animals and has been used with success in a few patients in doses of 2 to 4 gm daily. In one with the pneumonic form contracted in a laboratory, Huang and his associates had good results. The dosage is not established but probably rests between 1 and 3 gm daily in divided doses given intramuscularly.

Antiplague serum has its advocates but is of little value. It is expensive and its administration is complicated and it often causes a severe reaction and serum disease. Bacteriophage is of no value.

HOBART A. REIMANN

measured at the bedside, preferably with

than 1058 more fluid is needed. If actual measurements cannot be made judgment as to the amounts needed must be guided by the clinical response, blood pressure, pulse rate, consistency of the blood, and output of urine. Care must be taken not to give too much lest overfilling occur, signaled by restlessness, palpitation, substernal oppression, cough, or edema.

Sterile, pyrogen free isotonic solution of sodium chloride (9 gm sodium chloride to 1000 cc water) is the fluid of choice. Some clinicians prefer to add 5 per cent dextrose, but not more than 400 gm of glucose should be given in 24 hours. Thiamine chloride, 1 mg for every 25 gm of dextrose, may be

of injecting plasma for the shock like state is controversial.

ROUTINE CARE The management of a cholera patient is otherwise the same as for any severe infection of the gastro intestinal tract. Patients should be strictly isolated. Clothing, bedding and personal articles should be sterilized by washing with soap and hot water, by boiling, or with chemicals. Alvine discharges and vomitus must be disinfected with 1:1000 solution of mercury bichloride or other germicide before disposal in a sewage system. Otherwise they should be emptied into a deep covered pit, remote from any water supply or kitchen. Attendants must be taught to observe rigid rules of hygiene. Flies and vermin must be exterminated.

The patient should have a minimum of disturbance. During periods of chill and collapse the body should be covered and warmed to normal temperature with hot water bottles or heated coverings. Water and liquid or semisolid food may be given, if desired by the patient. Restlessness may be treated with barbiturate compounds or with morphine. The latter may be used for the severe pain of muscular cramps. Complications are uncommon but should be anticipated and treated.

DRUGS Digitalis or other cardiac and circulatory stimulants are not needed, unless heart disease itself is present. Medicaments such as purgatives, enemas, intestinal antiseptics, constipating agents, opium, specific immune serum, bacteriophage, and others are of no proved value and are not recommended.

Penicillin and streptomycin are of no value. Opinion differs as to the effectiveness of sulfadiazine. Chu and Huang gave sodium sulfadiazine intravenously and obtained good results, but Pasricha's group found sulfa

duced the mortality rate from 75 per cent to 37 per cent in otherwise well treated patients in hospitals and from 41 per cent to 18 per cent in patients in their homes where supportive treatment was not given. Bhatnagar used 20 to 30 gm of a new sulfonamide formaldehyde compound called '6257' and reported good results in all his patients. If the value of either sulfaguanidine or '6257' is confirmed, mass treatment will be greatly simplified if there is no need for injection of fluid. Further study of these drugs is indicated.

Convalescence Recovery, even without treatment, is often surprisingly rapid but rest in bed should be enforced reasonably for several days. Subsequent fatalities may occur suddenly, some of them perhaps from embolism. Fluid and soft, easily digested foods both preferably warm or hot, may be offered as soon as desired by the patient. Patients should not be released from control until their stool cultures no longer contain *V. comma*.

HOBART A. REIMANN

REFERENCES

- Bhatnagar S, et al. Chemotherapy of Cholera with a New Sulphonamide Compound ("6257") Laboratory Investigations and Field Trials. *Brit Med J*, 1:719, 1948.
 Chu L. W. and Huang C. H. Effect of Sulfadiazine on Cholera. *Am J Trop Med* 26:821 1946.

Treatment

TETANUS

That the treatment of tetanus is not particularly satisfactory is evident from the controversial nature of articles on the subject. Nevertheless, recognition of the limitations in the management of patients with clinical manifestations of tetanus serves to clarify some of the controversial issues and properly places emphasis upon those measures which provide the minimum of danger to the patient. At the same time, the unsatisfactory nature of treatment makes all the more important the widespread utilization of the recently demonstrated fact that tetanus is an entirely preventable disease.

Since only those patients who have not already a lethal amount of toxin in the central nervous system can be saved, practical treatment should be formulated: (1) to control life endangering spasms or convulsions while maintaining adequate oxygenation and hydration of the patient and (2) to prevent additional tetanus toxin from reaching the nervous system. At the same time, one should organize treatment so as to eliminate procedures which might prove fatal either because the procedure itself is inherently dangerous or because it may induce severe spasms.

Control of Spasms and Maintenance of Hydration and Oxygenation. Death from asphyxial spasms or exhaustion is prevented by sedation and by guarding the patient from all unnecessary stimuli. The latter measure entails strict seclusion in a quiet, darkened room with a minimum of handling of the

frequently repeated. Usually a fairly large initial dose is required followed by smaller maintenance doses. According to the severity of the disease, the initial dose may be 30 to 90 mg. per kilogram of body weight and the maintenance doses 10 to 30 mg. per kilogram. Sometimes difficulty is encountered because the solution is expelled from the rectum. Usually this is due to inadequate relaxation, either because no sedation has been given previously or because the interval between doses has been too long. The administration of sodium amytal intramuscularly or intravenously in amounts up to 1 mg. per kilogram of body weight will usually produce sufficient relaxation so that a solution of tribromethanol may be used. Considerable caution must be exercised in giving sedatives intravenously to patients with tetanus lest in one's haste to control a severe spasm an amount of the sedative be given which proves to be dangerously depressing once relaxation occurs. The use of dilute solutions injected slowly will diminish this hazard. In some cases of severe tetanus, sodium amytal may be needed to supplement the rectal medication, especially at times when severe spasms might be precipitated by necessary manipulations of the patient. Capsules of seconal, 100 to 500 mg. at a time, inserted into the rectum are a practical means of sedation in the milder cases or dur-

reaction of the patient afford the best guide as to the maintenance dosage of sedatives required.

Severe pain and great terror are engendered by the spasms of tetanus. These can be relieved by sedation in mild and moderately severe cases. Painful spasms cannot be safely eliminated at all times in severe cases. In such instances small to moderate doses of an analgesic such as 0.6 gm. of aspirin may greatly aid in the management of the patient. Demerol hydrochloride, 100 mg., with less respiratory depressant action may be preferable to morphine, although the latter has been used successfully in many cases.

The preteral administration of magnesium sulfate has numerous advocates, but with this drug the relief of spasms has not been as satisfactory as with the other drugs. Whereas alarming degrees

stantly balance the expected worth of each procedure against its possible disturbance to the patient.

The objective in sedation is to afford relief from spasms and convulsions without undue depression of the respiratory and cardiovascular systems. It is desirable to utilize agents which will maintain a fairly steady depth of sedation and a large degree of flexibility, because the pathway between life endangering spasm and serious depression of vital functions is frequently narrow. Solution of tribromethanol (avertin) has proved quite satisfactory when used in small amounts.

REFERENCE

Wu L, et al *Plague A Manual for Medical and Public Health Workers* Shanghai Weishengshu, 1936

LEPROSY

Prevention Since observation has suggested intimate and prolonged contact with a leper to favor transmission of the disease to others, a most important factor in prevention is the isolation of lepers during the active stages of the infection. Of 700 cases studied by Rogers, 80 per cent had lived in the same house with a patient, and 30 per cent had shared a bed with one. Other studies showed that only 3 to 5 per cent of exposed persons were infected. With reasonable care, however, the danger of transmission is small, especially to adults who observe hygienic measures. The patient should be instructed how to avoid infecting others and, if cooperative, is no serious menace except to infants. It is best to remove infants from leprous households. There appears to be a strong familial tendency or predilection to contract the disease when exposed to it. Patients who have recovered from leprosy clinically and who have no discharging lesions are regarded as non-infectious and may live unrestricted lives except for reporting for periodic examinations for evidence of relapse. The transmission of leprosy by way of tattooing was observed in 2 soldiers.

Treatment Patients are best treated in a leprosarium, such as the one at Carville, La., where the disease is best understood and managed by experienced and interested personnel. Efforts are directed to make life attractive and as free from restriction as is safe. The general health should be improved by measures akin to those needed for tuberculosis. Cleanliness, diversion, occupation,

improving the morale of patients. Frequent hot baths and a change of climate are often helpful.

According to McCoy, although segregation has not been proved to be an effective public health measure, patients with "open" leprosy should be isolated. Secretions and ex-

cretions should be destroyed by heat or otherwise.

SPECIFIC TREATMENT Antibiotics and the commonly used sulfonamide compounds have no effect in leprosy, except to control secondary pyogenic infections caused by bacteria sensitive to the effects of these agents. However, three new compounds, namely *promin*, *promizole*, and *diazone* are of value. Since they have been in use, the number of patients discharged as arrested cases from the National Leprosarium at Carville in 1946 was double and the death rate one half that of any previous year. The effects of *promin* and *diazone* are similar, but the latter has the advantage of being tolerated in oral dosage of 1 gm daily for long periods. According to Faget and his co-workers, *promizole* in doses gradually raised to 1 gm daily is well tolerated and clinical improvement occurs faster than after therapy with *promin* or *diazone*. Improvements in patients with advanced lepromatous leprosy may appear after 6 months or more of treatment. Further study is needed. Toxic reactions such as fever, malaise, hematemia, anemia, and others occur.

Chaulmoogra oil and its various derivatives are recommended by some observers but are considered as drugs of unproved value by the majority. They have little or no curative value and their unpleasant side effects probably outweigh any advantage which may occur from their use.

Röntgen ray or light treatments have at times a favorable influence. Large doses of vitamin B₁ (thiamine chloride) 100 mg intravenously, twice daily, are said to relieve the pain of neuritis.

Complications require appropriate medical, orthopedic, or surgical care.

HOBART A. REIMANN

REFERENCES

- Faget, G. H., and Erickson, P. T. Chemotherapy of Leprosy. *JAMA*, 136 451, 1947.
 Faget, G. H., and Fogge, R. C. Therapeutic Effect of Promin in Leprosy. *Pub Health Rep*, 60 1165, 1945.
 Faget, G. H., Fogge, R. C., and Johansen, F. A. Present Status of Diazone in Treatment of Leprosy. Brief Clinical Note. *Pub Health Rep*, 61 960, 1946.

TETANUS

That the treatment of tetanus is not particularly satisfactory is evident from the controversial nature of articles on the subject. Nevertheless recognition of the limitations in the management of patients with clinical manifestations of tetanus serves to clarify some of the controversial issues and properly places emphasis upon those measures which provide the minimum of danger to the patient. At the same time the unsatisfactory nature of treatment makes all the more important the widespread utilization of the recently demonstrated fact that tetanus is an entirely preventable disease.

Since only those patients who have not already a lethal amount of toxin in the central nervous system can be saved, practical treatment should be formulated (1) to control life-endangering spasms or convulsions while maintaining adequate oxygenation and hydration of the patient, and (2) to prevent additional tetanus toxin from reaching the nervous system. At the same time one should organize treatment so as to eliminate procedures which might prove fatal either because the procedure itself is inherently dangerous or because it may induce severe spasms.

Control of Spasms and Maintenance of Hydration and Oxygenation. Death from asphyxial spasms or exhaustion is prevented by sedation and by guarding the patient from all unnecessary stimuli. The latter measure entails strict seclusion in a quiet, darkened room with a minimum of handling of the patient even for examinations, bathing, feeding, obtaining laboratory specimens, and the administration of drugs. One must constantly balance the expected worth of each procedure against its possible disturbance to the patient.

The objective in sedation is to afford relief from spasms and convulsions without undue depression of the respiratory and cardiovascular systems. It is desirable to utilize agents which will maintain a fairly steady depth of sedation and a large degree of flexibility because the pathway between life-endangering spasm and serious depression of vital functions is frequently narrow. Solution of tribromethanol (avertin) has proved quite satisfactory when used in small amounts.

frequently repeated. Usually a fairly large initial dose is required followed by smaller maintenance doses. According to the severity of the disease the initial dose may be 30 to 90 mg per kilogram of body weight and the maintenance doses 10 to 30 mg per kilogram. Sometimes difficulty is encountered because the solution is expelled from the rectum. Usually this is due to inadequate relaxation either because no sedation has been given previously or because the interval between doses has been too long. The administration of sodium amytal intramuscu-

tion of tribromethanol may be used. Considerable caution must be exercised in giving sedatives intravenously to patients with tetanus lest in one's haste to control a severe spasm an amount of the sedative be given which proves to be dangerously depressing once relaxation occurs. The use of dilute solutions injected slowly will diminish this hazard. In some cases of severe tetanus sodium amytal may be needed to supplement the rectal medication especially at times when severe spasms might be precipitated by necessary manipulations of the patient. Capsules of secenal 100 to 500 mg at a time inserted into the rectum are a practical means of sedation in the milder cases or during the recovery period of more severe cases. Careful charting of the amounts of sedatives totaled every 12 hours and notes as to the reaction of the patient afford the best guide as to the maintenance dosage of sedatives required.

Severe pain and great terror are engendered by the spasms of tetanus. These can be relieved by sedation in mild and moderately severe cases. Painful spasms cannot be safely eliminated at all times in severe cases. In such instances small to moderate doses of an analgesic such as 0.6 gm of aspirin may greatly aid in the management of the patient. Demerol hydrochloride 100 mg with less respiratory depressant action may be preferable to morphine although the latter has been used successfully in many cases.

The parenteral administration of magnesium sulfate has numerous advocates but with this drug the relief of spasms is less definite, whereas clonidine is

sion of respirations has been noted quite frequently.

Curare has been suggested as an ideal agent for relieving the spasms of tetanus. When proper dosages and precautions have been determined this drug may have considerable value in tetanus but the evidence to date does not warrant its use except on an experimental basis by those experienced in its administration. The use of d tubocurarine in peanut oil and beeswax has diminished the need for frequently repeated doses. However in many cases the amount of curare required to control convulsions has dangerously depressed respirations. Bronchospasm secondary to the action of curare in liberating histamine in unanesthetized patients may be expected in some patients. Until the mechanism of the lethal effect of prolonged curarization observed in dogs has been explained its use in full doses over long periods of time cannot be recommended in cases of tetanus.

Cyanosis in a patient with tetanus may be due to a variety of conditions such as the accumulation of secretions in the pharynx, spasms of the glottis or respiratory muscles, excessive depression of the respiratory center or as the result of atelectasis or pneumonia. Placing the patient on his side or face down with the head low with or without gentle mechanical aspiration will relieve the first condition. Readjustment of the level of sedation will generally relieve the second and third conditions. When laryngeal and pharyngeal spasms are interfering with the passage of air a tracheotomy should be performed. Oxygen should be on hand at all times and should be given to any patient with cyanosis.

Satisfactory hydration of the patient during the period when oral fluids cannot be taken with safety may be accomplished by means of 5 or 10 per cent glucose in water and physiologic saline. To cover the obligatory losses of water from the lungs and skin and provide water for urine formation glucose in water should be given 125 cc per kilogram of body weight per day for an infant and gradually decreasing amounts for older children down to 30 cc per kilogram per day for an adult. Sufficient sodium and chloride will be provided by a total of 75 cc of saline for infants and up to 250 cc for

adults each day unless there is an unusual large amount of perspiration. The tendency is to give excessive amounts of sodium chloride to patients with tetanus. Daily b

to guide the fluid therapy.

When food can be taken by mouth safely a liquid high carbohydrate adequate caloric diet may be offered. Otherwise during the critical period of the first five to seven days the potential danger of tube feeding or an extensive program of intravenous feeding overshadows any benefit to the patient. Patients with tetanus maintained free from serious spasms well oxygenated and in good hydration readily tolerate the necessary degree of partial starvation whereas fatal spasms have resulted from injudicious attempts to maintain caloric equilibrium.

Urinary retention especially in adults may require catheterization of the bladder. If it should be done during the time when sedation is deep.

Competent nursing supervision is invaluable in the maintenance of a more or less heavily sedated patient with a minimum disturbance. As long as serious spasms occur no patient should be left alone.

Preventing Additional Toxin from Reaching the Central Nervous System. The results in many thousands of injured patients have conclusively demonstrated the efficacy of prophylaxis by means of adequate passive immunization. If these observations are accepted it follows that tetanus antitoxin alone in sufficient quantity will prevent toxin as yet unbound from reaching the central nervous system. The corollary is that other measures designed to prevent the spread of tetanus toxin from its site of elaboration on an

should be gauged by the severity of the disease as indicated by the length of the incubation period.

sodes of generalized muscle spasms occurred. Size of the patient should not be used to calculate the amount of antitoxin. In occa

sional severe cases up to 1 000 000 units of antitoxin may be needed

All too frequently serious reactions follow the administration of tetanus antitoxin especially in children The intramuscular route is the safest one for the administration of the serum but because the time factor may be important especially in severe cases one half of the antitoxin may be given intravenously to such patients Mild cases or patients believed to be sensitive to the serum used should not receive antitoxin intravenously Although the administration of antitoxin intrathecally provides some additional protection to experimental animals there is merely suggestive evidence of its usefulness in human patients with tetanus Intrathecal administration of tetanus antitoxin has caused death in some patients who in all likelihood would have survived their tetanus infections Therefore if the intrathecal route is used at all it should be reserved for only the most severe infections

Reactions to serum will be minimized by using highly purified concentrated serum carefully administered Individuals sensitive to serum may be detected from a history of previous administration of serum to the patient or of allergic manifestations in the patient or his family The ophthalmic test for sensitivity and an injection of solution of epinephrine hydrochloride (0.1 cc for infants to 0.5 cc for adults) with or without atropine (0.1 to 0.6 mg) probably should be used prior to serum administration Before a large amount of serum is given intravenously it is desirable to inject only 0.5 cc of a 1:10 dilution of the serum intravenously and to check the clinical condition of the patient and record his blood pressure for 20 minutes before proceeding For the early detection of thermal reactions the patient's temperature should be taken every 30 minutes for the first 3 hours after serum administration

Surgical Procedures and Chemotherapy
The proper surgical care of injuries irrespective of the presence of tetanus is essential when the nature of the injury is such as to require operative intervention but only those surgical procedures which would be recommended in the absence of tetanus should be performed An operation for the sole purpose of removing the presumed focus from

which toxin is being elaborated is unnecessary in the presence of circulating antitoxin as has been demonstrated by both experimental and clinical observations

The use of penicillin solely for its action on the tetanus bacilli is likewise unnecessary and is undesirably disturbing to the patient

The use of phenol parenterally for its supposed detoxifying action as recommended by F. C. C. is unsatisfactory in tetanus

Pneumonia This is still a serious complication of tetanus despite the availability of chemotherapeutic agents The inciting factors of hypostasis and inadequate pulmonary excursions can be diminished by frequently changing the patient's position and by using sufficient sedation to prevent rigidity of the thoracic cage and by avoiding undue depression of respirations from excessive sedation Periodic inhalations of oxygen with 10 per cent carbon dioxide may be used if well tolerated It is probably better to reserve the use of sulfonamides and penicillin for treatment of pneumonia if it develops rather

After Care Two points in the management of patients recovering from tetanus deserve mention The first is that all patients even those with mild tetanus should have a roentgen examination of the spine before being discharged from the hospital in order to detect compression fractures of the vertebrae The second is that all patients who have received antitoxin should subsequently be actively immunized against tetanus

render a second use of serum more dangerous

Prophylaxis Study of the nature of the injuries resulting in tetanus in civilian life reveals that only a program of active immunization which will produce and constantly maintain a high level of immunity will prevent this disease All cases of tetanus cannot be prevented by reliance on immediate surgical treatment of injuries nor by passive immunization with antitoxin nor by the

type of active immunization which depends upon the use of booster doses of toxoid at the time of injury, even though each of these measures is effective when applied. Many cases of tetanus occurred either when no injury was recognized or when the injury was so trivial that these methods of preventing tetanus would not ordinarily be utilized. The remarkable success in protecting military personnel from this disease has unequivocally demonstrated that active immunization against tetanus is one of the most worthwhile measures in preventive medicine.

Active immunization is especially recommended for children, farmers and artisans. It is particularly important to immunize actively persons naturally allergic to horse serum or who have received horse serum therapeutically. The favorable publicity given immunization procedures during recent years should be utilized to promote this effective preventive measure.

For children and adults three injections of 1 cc of fluid toxoid given at 1 to 3 months intervals and followed by restimulating injections of 0.5 to 1 cc of toxoid every 2 years is the most widely recommended program.

For primary immunization in infants most workers agree that alum precipitated or aluminum hydroxide adsorbed tetanus toxoids combined with diphtheria toxoid and maybe also phase I *Hemophilus pertussis* vaccine is the preparation of choice for basic immunization. If combined diphtheria tetanus alum precipitated or aluminum hydroxide adsorbed toxoids are used 1 cc of the preparation is given when the patient is 5 to 11 months old and again 3 months later, and after another 3 months 1 cc of tetanus toxoid alone is given. Combined vaccines employed during the first quarter of the first year are producing favorable immunization responses and may become the recommended basic immunization procedure after more clinical trials. One year after the basic immunization 0.5 cc of alum precipitated or aluminum hydroxide-adsorbed tetanus toxoid should be injected and repeated every 2 years.

Although basic immunization followed by restimulating injections every 2 years provides adequate immunity in nearly all cases,

caution dictates that a booster dose of fluid tetanus toxoid be given whenever an injury from which tetanus is particularly prone to develop is sustained.

Although prophylaxis with tetanus antitoxin cannot prevent all cases of tetanus when properly utilized its efficacy is unequivocal. It is obvious that passive immunization should be used whenever a patient not actively immunized presents himself for treatment of an injury recognized as a potential source of tetanus. Since 1500 American units of antitoxin have been inadequate occasionally, at least 5000 units should be used. For extensive injuries with a great deal of devitalized tissue or if a considerable period of time has elapsed between the injury and the prophylactic treatment two to four times that amount of antitoxin should be given.

EDWARD L. PRATT

REFERENCES

- Abel J J and Hampil B. Researches on Tetanus. Some Historical Notes on Tetanus and Commentaries Thereon. *Bull Johns Hopkins Hosp* 57: 343 1935.
- Dietrich H F. Tetanus in Childhood with Special Reference to Treatment. *Am J Dis Child* 69: 693 1940.
- Francisco R. Clinical and Epidemiological Study of Tetanus in Puerto Rico. Study of 100 Cases Seen at Arecibo Charity District Hospital in 2 1/2 Year Period. *Clinics* 3: 873 1944.
- with Special Reference to Methods of Fievet and Plan for Evaluating Treatment. *JAMA* 129: 1243 1945.
- Spaeth R. Clinical Study of Tetanus. *Am J Dis Child* 60: 130 1940.
- Thompson W D Jr and Friedman L. Efficacy of Phenol and Tetanus Antitoxin in Treatment of Experimental Tetanus. *Surg Gynec & Obst* 72: 860 1941.

ANTHRAX

The results of modern therapy can best be appreciated from the figures collected by Smyth. In 25 cases with no treatment because of wrong diagnosis the fatality rate

was 88 per cent while in 749 treated cases the death rate was 7.4 per cent. With the advent of the antibiotics there is hope for further reduction in the mortality rate from anthrax. Two series of penicillin-treated cases have already been reported with no deaths by Ellingson and his associates and Griffith and his co-workers. In our last 78 cases we had no fatalities.

Cutaneous Anthrax. This should no longer be considered a surgical problem. There is no justification for incision, excision, or cautery of the skin lesion. Local treatment should consist of rest of the affected part by

control secondary pyogenic infection of the ulcer as indicated. Systemic treatment should be started as soon as the disease is suspected and should not await bacteriologic confirmation, but smears and culture of the region should always be taken prior to therapy. The results are definitely influenced by the early recognition of the disease and the institution of prompt and adequate treatment. This may consist of (1) antibiotics (2) sulfonamides (3) neoarsphenamine (4) antianthrax serum (5) miscellaneous.

Treatment should be continued until the edema has cleared, cultures from the lesion have become negative for *B. anthracis*, and signs of toxicity, fever, rapid pulse, malaise have subsided. Judged by the rapidity with which these criteria are met, penicillin is the drug of choice. However, it must be noted that the course of development of the "pus tle" through the stages of papule, vesicle, and eschar formation is not affected by any form of treatment; regional adenopathy may persist after healing of the ulcer has set in and the patient is well on the road to recovery.

Penicillin. Both *in vitro* and animal experiments have conclusively shown that *B. anthracis* is sensitive to penicillin, but the degree of sensitivity varies with different strains. Furthermore, the *in vitro* sensitivity

cultures with 60,000 units of penicillin intramuscularly in each of five doses followed by 30,000 units every 3 hours by the same

route. Their total dosage ranged from approximately 1,000,000 to over 4,000,000 units. All patients recovered. Previously, Murphy et al. reported studies on 3 cases and found that a total of 100,000 units of penicillin is certainly the minimal effective dose in the uncomplicated case of cutaneous anthrax. They concluded that at least a total of 200,000 to 400,000 units of penicillin given at the rate of 100,000 units per day should be administered to the average adult and this amount should effect a prompt and satisfactory therapeutic response. Similar results were reported by Stott, Weinstein, and Oliver. Mann and Griffin et al. treated 17 cases with 100,000 to 300,000 units of penicillin every 3 hours intramuscularly with a total average of 12,882,940 units during the hospital course. All face and head lesions also received sulfadiazine. One case of meningitis was supplemented with antianthrax serum. The authors felt that because of the scarcity of reported cases it was safer to administer large doses of penicillin.

We prefer to give a large initial dose of 100,000 units of penicillin intramuscularly followed by 20,000 to 50,000 units every 3 to 4 hours depending on the severity of the case. As soon as the edema recedes (24 to 72 hours after penicillin therapy is begun) the dosage is decreased to about 20,000 units every 4 hours; this is then continued for a day or two. In the early part of treatment an occasional patient may show increase in the erythema and swelling around the lesion. This however subsides within 24 hours. Adenopathy may persist for a few days or weeks after the patient is otherwise well; its presence is no indication for continued therapy. We recently treated a case of anthrax of the face with procaine penicillin in oil. A single daily injection of 600,000 units was

tory care is possible.

Streptomycin. In experimental infections of mice, Miller et al. found streptomycin to be highly effective in doses of 500 to 1600 units daily per 18 to 22 gm of mouse. This is within the limits of maximal dosage in man. Also Housewright et al. confirmed in anthrax infections in mice the reported addi-

tive effect in vivo of streptomycin and penicillin. No clinical studies have as yet appeared on human infections treated with streptomycin. Although the Council on Pharmacy and Chemistry in its report on this antibiotic stated that "It is occasionally effective in anthrax," it is likely, in view of the animal experiments, that streptomycin will be of value if given in doses of 1 to 2 gm daily. However, the greater risk of toxic reactions and its relative expensiveness makes this drug quite inferior to penicillin.

AUREOMYCIN This new antibiotic has been tried by the writer in a case of anthrax of the wrist with satisfactory results. The edema, erythema, and signs of toxicity were controlled within 48 hours after therapy was instituted but bacteriologic control was not achieved until the fourth day. As expected the "pustule" was not affected in its course of development. This patient received 0.75 gm of aureomycin orally every 4 hours until the edema began to recede, thereafter, the dose was reduced to 0.5 gm every 6 hours.

In vitro tests showed that *Bacillus anthracis* recovered from the lesion was sensitive to aureomycin, growth being inhibited by 0.025 microgram per cubic centimeter. Its ease of administration, absence of reactions, and the fact that it allows for ambulatory management of cases of anthrax makes aureomycin a welcome addition to our therapeutic armamentarium.

SULFONAMIDES Both experimental and clinical studies confirm the value of sulfa-

drugs in the treatment of anthrax. If adequate blood levels, the drug is given orally for 2 or 3 days. Alkalinization and adequate urinary output are secured and frequent urinalysis and blood counts are done. If the edema is not controlled by the third day, a change in therapy is indicated. Until the advent of penicillin, we preferred the sulfonamides for the treatment of cutaneous anthrax even though their effect on anthrax edema was not as prompt as that produced by optimal doses of antianthrax serum. The morbidity rate was definitely decreased, the cost per patient was lowered and ambulatory care was possible.

NEOARSPHENAMINE In our hands, the sulfonamides were found to be superior to

neoarsphenamine. The latter drug was given by us in addition to antianthrax serum to a group of 10 patients without any effect upon the course of the disease or its morbidity. Similar findings were reported by others. However, Lucchesi and Gildersleeve definitely expressed a preference for neoarsphenamine and recommended an initial dose of 0.6 gm followed by 0.9 gm on each of 2 suc-

no deaths.

ANTIANTHRAX SERUM Following the demonstration of the therapeutic value of penicillin and sulfonamides the use of specific serum has been practically abandoned. Most pharmaceutical firms have ceased to manufacture it, yet occasionally one encounters a virulent infection which resists all forms of available therapy and under such circumstances, one wishes for a potent horse serum.

When used it should be given in large amounts to secure optimal results. An initial dose of 300 to 500 cc intravenously, repeated in 12 to 24 hours, may be needed to control the spread of the edema. Thermal and sensitization reactions and serum sickness are frequent complications following its use.

MISCELLANEOUS Local applications of small doses of roentgen rays, immunotransfusion, ordinary horse serum injections, etc. have all been used in the treatment of anthrax with debatable or indifferent results. It is obvious that supportive treatment and good nursing care are required in this as well as in any other disease.

Internal Anthrax In this country, internal anthrax is rather infrequent. We have seen only one case of pulmonary anthrax. Bacteremia with secondary localization in the lungs and meninges has been reported by Lucchesi and Gildersleeve, Weinstein and Oliver, and Shanahan et al. In the presence of anthrax pneumonia or systemic invasion much larger doses of penicillin than those recommended for the cutaneous form should be used. In addition, sulfadiazine should be administered by mouth or intravenously. In meningitis, the intrathecal injection of penicillin, 20,000 to 30,000 units repeated if necessary every 12 to 24 hours, is indicated, in addition to parenteral therapy. Proper

precautions should be used to avoid untoward reactions and cross infection of the cerebrospinal system

HERMAN GOLD

REFERENCES

- Abraham C P et al Further Observations on Penicillin *Lancet* 2 177 1941
- Council on Pharmacy and Chemistry Streptomycin *JAMA* 135 839 1947
- Ellingson H V et al Cutaneous Anthrax Report of 25 Cases *JAMA* 131 1105 1946
- Fleming A On Antibacterial Action of Cultures of a Penicillium with Special Reference to Their Use in Isolation of *B. Influenzae* *Brit J Exper Path* 10 226 1929
- Gold H Anthrax in *Nelson & Loose Leaf Medicine* New York Thomas Nelson & Sons 1947 Vol I p 641
- Gold H Anthrax Review of 60 Cases with Report on Therapeutic Use of Sulfonamide Compounds *Arch Int Med* 70 785 1942
- Gold H Aureomycin in the Treatment of Anthrax (To be published)
- Griffin J R Shanahan R H and De Angelis C E Treatment of Cutaneous Anthrax with Penicillin *New York State J Med* 43 1718 1945
- Heilman F R and Herrell W E Penicillin in Treatment of Experimental Infections with *B. anthracis* *Proc Staff Meet Mayo Clin* 19 492 1944
- Housewright R D Berkman S and Henry R J Conference in Antibiotic Research Antibiotics Study Section of NIH Feb 1 1947 Washington DC
- Lucchesi P F and Gildersleeve N Treatment of Anthrax *JAMA* 116 1508 1941
- Mann G N Penicillin in Treatment of Human Anthrax *J Roy Army M Corps* 89 79 1947
- McCullough A and von Auersperg A P Effect of Penicillin and Antianthrax Serum in Experimental Anthrax *Am J Clin Path* 17 151 1947
- Miller E S et al Chemotherapy of Experimental Anthrax Infections *J Immunol* 53 371 1946
- Murphy T D La Boccetta A C and Lockwood J S Treatment of Human Anthrax with Penicillin Report of 3 Cases *JAMA* 126 915 1944
- Schabel F M Jr Reames H R and Housewright R H Use of Sulfadiazine and Penicillin for Treatment of Experimental Anthrax *J Infect Dis* 79 141 1946
- Shanahan R H Griffin J H and von Auersperg A P Anthrax Meningitis Report of Case of Internal Anthrax with Recovery *Am J Clin Path* 17 719 1947
- Smyth H F Anthrax Its Diagnosis and Treatment *Occup Med* 2 8 1946
- Stott H Treatment of Human Cutaneous Anthrax with Penicillin *Brit M J* 2 120 1945
- Weinstein L and Oliver C E Treatment of Human Anthrax with Penicillin *Am Pract* 2 533, 1945

GLANDERS

Glanders in man as in equine animals varies from an acute fulminating infection with septicemia to a chronic debilitating process with multiple lesions in the skin and viscera. The acute fulminating form has seldom been diagnosed before death and treatment has been symptomatic and ineffective. Treatment has been more successful in milder acute forms and in chronic glanders.

Sulfadiazine is reported to be the most effective of the chemotherapeutic drugs in vitro and in vivo tests. Fifty per cent of animals recovered when treated for 7 days and 100 per cent recovered when therapy was continued for 20 days. Sulfathiazole, sulfamerazine and sulfanilamide are somewhat less effective in vitro and have not been

used against a subacute form of the disease in man. Streptomycin, although moderately effective in vitro, had no effect on the experimental disease in hamsters.

In 6 cases of acute human glanders occurring in laboratory personnel, recovery took place after treatment with sulfadiazine. It is felt that the most effective therapeutic regime is as follows: As soon as blood culture or serologic tests indicate a diagnosis of glanders, the patient is given 5 gm. of sodium

forced fluid intake and in reducing drug complications. The strong tendency of the disease to form latent foci of infection which later become reactivated is best combated by administering intensive and uninterrupted therapy early in the course of the disease. Complete bed rest during therapy and a prolonged convalescent period permitting only light activity are important adjuncts. A well balanced diet with supplementary vitamins should be maintained during the acute illness and through the prolonged convalescence for maximum promotion of healing. The patient should be examined monthly for at least a year after apparent recovery. The development of a temperature elevation, skin pustules, localized chronic lymphadenitis, hepatomegaly or splenomegaly,

patchy pneumonic infiltration, or a sudden rise or precipitous fall in serum antibody titer indicates a probable recurrence of the disease in a subacute or chronic form

Chronic glanders is resistant to all forms of therapy. Although the mortality rate is high, a small percentage of patients have recovered after a long illness. Cox, Bristow, and White have made reports which claim benefit from the use of autogenous vaccines, and Watson from "immune serum, mallein, heavy metals, iodides, and quinine." The value of these methods has never been convincingly demonstrated. Many cases were treated surgically with multiple incisions of the abscesses and sinuses, and excision or amputation of infected areas but with no lasting benefit. No reports have been found of treatment of chronic glanders with sulfadiazine. Treatment of chronic experimental glanders with sulfadiazine for 20 days resulted in a remission of the infection during therapy, but in the majority of the animals a fatal relapse occurred weeks or months after therapy was discontinued.

Chronic glanders would probably best be treated with a long period of complete bed rest as in tuberculosis and a course of sulfadiazine therapy continued for 2 to 3 months if the drug can be tolerated. Since it has been shown that *Malleomyces* organisms in vitro develop sulfadiazine resistance rather easily, administration of the drug in small doses or in intermittent courses should be avoided whenever possible. Surgical drainage of fluctuant abscesses is always indicated. Wide excision or amputation of infected parts may give temporary benefit but is chiefly a palliative measure since foci of infection are widespread. Although antibodies can be demonstrated in chronic glanders and in vaccinated animals by agglutination, precipitation, and complement fixation techniques, attempts to demonstrate a definite active or passive immunity have been unsuccessful. Autogenous vaccines and antisera may be tried as adjuncts of therapy but are of doubtful benefit. A state of hypersensitivity in glanders can be demonstrated by a tuberculin-like skin reaction to mallein. Reports of benefit by desensitization therapy, however, have never been confirmed. Three to 5 gm of sodium or potassium iodide by intravenous or oral routes may be ex-

pected to be of some benefit in aiding resolution of the semicaseous or suppurative lesions. Prolonged rest, adequate fluid balance, a well balanced diet with supplementary vitamins, and other general supportive measures are important as in any chronic disease. Patients with apparent clinical recovery must be followed carefully for 1 or 2 years for signs of relapse.

be useful in glanders

WINSTON R MILLER

REFERENCES

- Bristow, A. T., and White, B. A Case of Chronic Glanders Treated by Autogenous Vaccine with Recovery. *New York State J Med* 10:236 1910.
Cox, C. D. Personal Communication. Unpublished Data on a Case of Subacute Glanders in China.
Crump, W. C. Chronic Glanders in Man. Report of a Case. Patient Treated with Glanders Vaccine. Apparent Cure. *JAMA* 56:1379 1911.
Howe, C., and Miller, W. R. Human Glanders. Report of 6 Cases. *Ann Int Med*, 26:93 1947.
Miller, W. R., Pannell, L., and Ingalls, M. S. Experimental Chemotherapy in Glanders and Melioidosis. *Am J Hyg*, 47:205 1948.
Watson, E. A. Serum Therapy of Glanders with Special Reference to Glanders in Man. *J Am Vet Med A*, 64:140 1923-24.

MELIOIDOSIS

The recent report by McDonald and Varney of a case of chronic melioidosis in this country has aroused interest in a disease which formerly had been contracted only in southeastern Asia. The more common acute septicemic form of the disease is rapidly fatal and seldom diagnosed before death. There are no reports of treatment of this form of the disease with sulfonamides. Recovery occurred in 2 cases of subacute melioidosis seen by Harris et al., limited to the respiratory tract after a total of 23 days' treatment with sulfathiazole and/or sulfamezathine. In several cases of chronic melioidosis a remission occurred during 10 to 15 day courses of sulfadiazine, sulfathiazole, or sulfamethazine, but all relapsed after therapy was discontinued, according to Harris et al. and Grant and Barwell.

Sulfadiazine is effective against the acute experimental disease in hamsters. When treatment was continued for 21 days 100 per

cent of the animals recovered. Penicillin has been shown to be completely ineffective against *Malleomyces pseudomallei* in vitro against acute experimental melioidosis in hamsters and against acute and chronic melioidosis in man as reported by the authorities in the References. Streptomycin showed a transient bactericidal effect in vitro but was ineffective in treatment of the acute experimental disease and in the chronic disease in man.

It is felt that sulfadiazine will give marked benefit in acute human melioidosis if treatment is instituted early. As soon as the disease is suspected 5 gm of sodium sulfadiazine should be given intravenously fol-

lowed by 4 hours and a forced fluid intake aid in reducing urinary drug complications. Continued signs of active infection during therapy indicate a shift to a subacute or chronic form of the disease and treatment should be prolonged accordingly.

Chronic melioidosis like chronic glanders is characterized by multiple lesions in the skin and viscera which vary from tiny granulomas to pyogenic abscesses and draining sinuses. To be of maximal benefit sulfadiazine should therefore be administered in full therapeutic dosage for long periods. It is felt that the patient should be kept at absolute bed rest and given sulfadiazine in 1 gm doses every 4 hours for 2 to 3 months or until severe drug toxicity develops. In a disease which is 95 per cent fatal a mild or moderate degree of drug intoxication need not require cessation of therapy. Intermit- tent therapy or treatment with small dosage tends to encourage development of drug resistant strains. The best possibility of recovery depends on early diagnosis and

be given every 4 hours with a forced fluid intake. Three to 5 gm of sodium or potassium iodide daily given intravenously or by mouth aid resolution of the semigranulomatous or suppurative lesions. Antiserum autogenous vaccines or whittomine may be tried as an adjunct of treatment but are of doubtful

value. Incision of localized abscesses and obstructed sinus tracts is indicated to establish drainage. Wide excision, cauterization or amputation of infected areas may be temporarily beneficial but do not result in cure. Cases of apparent recovery should be examined frequently since relapse may occur as long as 1 or 2 years later.

The efficacy of aureomycin against many gram negative organisms offers hope that it may be beneficial in melioidosis.

WINSTON R. MILLER

REFERENCES

- Cox, D. C. and Arbogast, J. L. Melioidosis. *Am J Clin Path* 15:567, 1945.
Grant, A. and Barwell, C. Chronic Melioidosis: Case Diagnosed in England. *Lancet* 1:199, 1943.
Harnes, E. J. et al. Melioidosis Treated with Sulfonamides and Penicillin. *Lancet* 1:383, 1949.
McDowell, F. and Varney, P. L. Melioidosis: Report of First Case from Western Hemisphere. *JAMA* 134:361, 1947.

120 1063 1946

TUBERCULOSIS

Medicine is half a science and half an art. The term "science" implies change and an "art" is something that is done differently by each practitioner. At the present time the science of medicine is advancing with extreme rapidity and in the treatment of tuberculosis a disease of great variety in which psychological, social and economic factors play an important part, the element of art is great. Each physician has prejudices and preferences which are the result of his particular experience and his personal evaluation of almost invaluable factors. For the first reason, every textbook on medicine is certain to be out of date by the time it is published and for the second reason, every textbook on tuberculosis is bound to be an expression of only one of many points of view. Whoever reads a textbook should remember that the science has advanced since the text was prepared and that the art is personal and must be learned by long experience.

The Types of Treatment. Pulmonary tuberculosis has been known and recognized

since the earliest times and thousands of medicines and regimens have been recommended for its treatment. The failure of all remedies stimulated the quest for new ones, and throughout the centuries, in steady succession, everything from drinking goat's milk or ox blood to residing in this or that particular climate was heralded as a cure. In spite of this, until less than 90 years ago the disease was considered regularly fatal and physicians prescribed and patients tried this or that treatment desperately and hopelessly. Hippocrates prescribed mountain air and Galen sent his patients to drink goat's milk at his farm on the hills above the Bay of Naples. When Keats spat blood he was advised to take a walking trip in Scotland. Chopin was told to go to the Island of Minorca and Laennec following Galen, took himself to the coast, where, as he walked by the sea and subsisted upon goat's milk, he watched the progression of the physical signs in his own chest.

Since 1868 when Bremer and Deitweiler first demonstrated the efficacy of rest in bed, three true remedies have been found. These are rest in bed, collapse or excision of the affected portions of the lungs, and, recently, streptomycin. Of all the thousands of measures which have been suggested and tried those are the only three which have been proved to have any value. The laity and some of the medical profession still have faith in particular climates and some patients still insist on having goat's milk but most now recognize that a well balanced general diet is all that is important and that any climate is satisfactory save a tropical one in which excessive heat and humidity render existence, even of the well, difficult and precarious. Patients will recover equally well and quickly in all temperate climates and at all altitudes and on any adequate and well balanced diet. They will not recover at all save rarely and by chance, without bed rest, or bed rest and streptomycin, or bed rest, streptomycin, and collapse or excision.

Bed Rest. Rest in bed is effective in the treatment of pulmonary tuberculosis chiefly because it decreases the motion of the lungs. It favors, as does the rest of any infected part, the localization and control of the infection and the repair of the injury to tissue. In the lungs also it discourages the aspiration of

infected secretions into unaffected pulmonary areas.

Rest in bed decreases the motion of the whole of the lungs by approximately 75 per cent and of the parts affected by disease by a still larger amount. The movement of the lungs is in proportion to the oxygen requirements of the body, and at complete rest these are not more than one fourth of what they are under full body activity.

Rest in bed is selective for the diseased portions of the lungs because these are less elastic and therefore less easily moved than the normal parts. If the lungs are being used little diseased areas move even less and it is only when motion is exaggerated that they are brought into full play. Rest in bed may be made still further selective by having the patient lie on the affected side or by applying a splint to one half of his chest or by having him hold a shot bag over the affected portion.

Recently evidence has been offered that the blood supply to the upper parts of the lungs is appreciably reduced when an individual is in the upright position. This has been advanced as the reason for the preference of tuberculosis for the apices, and it has therefore been suggested that the recumbent position, by increasing the flow of blood to the affected areas, favors healing.

The patient's position in bed is important for other reasons. Postural drainage, which is desirable in lung abscess and bronchiectasis, is dangerous in tuberculosis because it favors the spill of infected secretions into the unaffected lung areas which in postural drainage are usually made dependent. For this reason the patient with tuberculosis should be cautioned against lying on his better lung. The advantages of better drainage are much less than the danger of spread of the disease.

Rest in bed is effective in proportion to bodily activity. Some patients can be very active in bed. Many cautious phthisiologists insist that patients with acute tuberculosis

sobbing cause excessive motion of the lungs. For this reason temperatures are always higher on visiting days and for this reason patients with acute disease should always be in private rooms. A good spell of sobbing

such as women frequently indulge in is extremely dangerous and is often followed by an exacerbation or spread of the disease.

Part of the value of sanatorium care and rest in bed is the regularity of the life. The body at the autonomic level is greatly affected by habit. An individual eats, digests, excretes, rests, and sleeps best if he does these things at the same time each day. For this reason patients should be upon a rigid

schedule for a few weeks; he follows it out of desire—he relaxes into it as it were—and mentally and physically exists with much less effort and with much greater efficiency. At certain times of the day his whole body becomes ready and eager for food or rest or sleep, and what has become habitual becomes easy and desirable.

Rest in bed is still the basis of all treatment of pulmonary tuberculosis. It should precede, accompany, and follow all measures of collapse or excision. It is the only treatment which affects all of the foci of tuberculosis in both lungs equally, and only after the disease has been rendered quiescent by rest are the other measures apt to be successful and uncomplicated. It should be complete and should be persisted in in curable cases as long as the sputum is positive simply because bodily activity favors exacerbation and extension.

Rest in bed should be complete in proportion to the acuteness of the disease. Truly acute exudative and febrile cases should be on absolute bed rest in private rooms. As the acute stage passes, they may tolerate complete rest in a double room or a ward, and later may be allowed bathroom privileges, but in all cases while bed rest is being used these should be the limit of privileges granted until the lesions are closed and the sputum negative.

The improvement from bed rest decreases steadily with time. It is greatest in the first month, less in the second, still less in the third, etc. Maximal benefit has usually been obtained in from 4 to 8 months. From this time on cavities rarely decrease in size and cure from simple rest rarely occurs. The time has come then to resort to whatever measure of collapse seems indicated.

Rest in bed should be in a sanatorium. Only there where all are on the same regimen can discipline be enforced and only there can the patient be under the close observation of the physician who must study and observe him from week to week and month to month so that he may be able to vary the treatment as indicated and apply collapse when that becomes advisable or necessary. And only in a sanatorium can a patient absorb an understanding of the seriousness of the disease with which he is afflicted and the measures which are necessary for recovery.

It is important that those with small lesions see people coming back with recurrences that they see some die of tuberculosis and others undergoing serious operations.

Most individuals and some inexperienced physicians believe that patients will rest as well at home as in a sanatorium. The patient who will do so is extremely rare. Strict bed rest is bitter medicine to take and the individual who will discipline himself to it at home is extremely rare. The physician's first function therefore is to convince the patient that he must go to a sanatorium and in nearly every case he must do this against the patient's strong desire and his many arguments and objections. But unless the physician succeeds in this first step, he is apt to fail in his entire purpose.

Collapse Therapy. In 1822 James Carson, an English physician, pathologist, and physiologist, made the statement that if certain types of pulmonary tuberculosis were ever to be cured, it would be by collapsing the diseased lung. Carson was the first to measure the intrapleural pressure. He reached his conclusion concerning tuberculosis from his realization that the lungs were continually stretched to fill the thorax and from his observation in performing necropsies that the chief obstacles to the healing of tuberculosis were the cavities which were prevented from closing by the stretching of the lungs. He suggested both artificial pneumothorax and thoracoplasty, and although it was 60 years before collapse was applied clinically, his article foreshadowed the second great advance in the treatment of tuberculosis.

Between 1852, when Forlanini first used artificial pneumothorax, and the present time, not only have pneumothorax and

thoracoplasty been perfected but also artificial paralysis of the diaphragm extrapleural pneumonolysis internal pneumonolysis pneumoperitoneum and Monaldi's drainage. Each of these methods of collapsing and resting the lung and closing cavities has proved to be a valuable addition to the armamentarium. Each has its particular uses and all together combined with bed rest and more lately with streptomycin have made it possible to cure or bring under control all save the most advanced cases of pulmonary tuberculosis. In considering them it is important to bear in mind that their great function is solving the major problem in the treatment of tuberculosis the closure of cavities.

Collapse of the lung sufficient to close all cavities is a specific remedy for tuberculosis. The local rest and the approximation of the walls of the cavities will produce arrest of the disease in practically every case. In a text concerned only with treatment this statement is sufficient. It is not necessary to consider the precise reasons for the effect. It is necessary to consider the particular advantages and disadvantages of each form of collapse and the particular indications for its use.

THE INDICATIONS FOR COLLAPSE THERAPY

In general the methods for collapsing and resting the lung may be divided into two classes i.e. those which are so simple and safe that they may be used early to hasten and assure recovery and those major surgical procedures which probably should be used only when all other methods of treatment have failed and permanent collapse is absolutely necessary. In the first group are phrenic nerve operations artificial pneumothorax and pneumoperitoneum and in the second are thoracoplasty extrapleural pneumonolysis and Monaldi's drainage. Excision will be considered under a separate heading.

In the treatment of tuberculosis and in the application of collapse measures there are many matters which are and always will be controversial. Where there are so many possible sequences and combinations of treatments where judgments based on accurate statistics are so difficult to secure and the factors to be balanced against each other are so often in different categories it is impossible for all to agree and it is not good

that they should. It will always be difficult to decide whether in any particular case the risks incident to artificial pneumothorax are preferable to a year or two of invalidism or whether the extended slight hazards of "air" are preferable to the definitive collapse of a thoracoplasty which carries with it the permanent psychologic handicap of an irreversible alteration in the shape of the body. In the long run each man on the basis of his own experience and his human understanding of each particular patient must make his own decisions and mix and apply his treatments to accomplish the desired result in consideration of the particular type and extent of the disease in the particular patient.

PHRENIC NERVE OPERATIONS. Induced paralysis of one half of the diaphragm is the simplest and safest of all collapse measures. If it is at all indicated there is no good reason for not using it. The only contraindication is a situation where the reduction in vital capacity would eventually interfere with some more effective type of collapse.

While it is the least drastic of all collapse measures it is also the least likely to be

effective. The results seems to have little effect and in others it is followed by the rapid closing of cavities. The occasional dramatic results and the probability that in every case it at least favors the closure of cavities are good reasons for using it quite generally.

The effectiveness of phrenic nerve block varies with the location of the lesions in the lung. One would expect it to give the best results in lesions in the base. For some reason concerned probably with the evacuation of secretions this is not so and these lesions are the ones least likely to be favorably influenced. It has more chance of closing infracavicular cavities and is almost specific for those close to the hilus and particularly for those posterior to the hilus in the apex of the lower lobe.

For unilateral or chiefly unilateral disease it is reasonable to block the phrenic nerve at the start of treatment in addition to the bed rest and streptomycin therapy. One can feel confident that it will do no harm in some cases the result will be dramatic, and in every

case it will favor the closure or the reduction in size of cavities

If phrenic nerve block is followed by closure of cavities and arrest of the disease it should be repeated each 1 or 2 months for a year or two or should be made permanent. Prior to 1935 all phrenic nerve operations either severed or extracted the nerve. Many of these patients have remained well and almost none has experienced any permanent inconvenience.

Phrenic nerve block has been advocated in conjunction with artificial pneumothorax. The adherents of this practice believe that it reduces the respiratory pressure changes in the pneumothorax space, increases the interval between refills and in general aids appreciably in the rest and relaxation of the lung.

Blocking the phrenic nerve at the end of a course of pneumothorax is a reasonable procedure. It favors the re-expansion of the lung and decreases the tension which will be exerted on the diseased areas. Immediate recurrences are less likely and less common if this is done.

If the phrenic nerve is blocked when an unsuccessful pneumothorax is abandoned the results are often dramatic. A cavity which has remained suspended for many months may suddenly close. Why this is so is uncertain. It is certain that it happens so often that it cannot be explained as mere chance. The procedure is always worth trying.

PNEUMOPERITONEUM The injection of air into the peritoneal cavity elevates the diaphragm and relaxes the lungs. If one half of the diaphragm has been paralyzed it greatly exaggerates the effect of this operation. It has the great advantage of being almost completely safe and of having few complications. The only good reason for not using it early in any case in which it is at all indicated is that its value is still questionable and that it commits one to a course of treatment which one may feel impelled to continue for a long period.

The results of pneumoperitoneum are not as dramatically demonstrable as are those of pneumothorax and thoracoplasty. The procedure is an adjunct to complete bed rest and its effects are gradual and difficult to distinguish from those caused by rest and

streptomycin. For this reason its position in the armamentarium is still a matter of controversy. It has its enthusiastic adherents who prefer it to pneumothorax and its doubters and detractors who do not use it at all. If it lacks the complications of pneumothorax it also lacks its great effectiveness in hastening and assuring recovery. It seems definitely indicated in far advanced bilateral disease in which pneumothorax is impossible. It may possibly be of much wider value when used early in many other cases in which like phrenic nerve block it may, with bed rest and streptomycin aid in the closing of cavities which would not close without it. In this manner alone it is conceivable that in many cases it can prevent the ultimate necessity for major surgical collapse.

ARTIFICIAL PNEUMOTHORAX Artificial pneumothorax the first of all the collapse measures to be developed and perfected is still the most effective and the most widely applicable. The direct and variable collapse which it produces closes cavities quickly and completely and puts the diseased portions of the lungs at almost complete rest. It converts the sputum quickly and does hasten and assure recovery. In most cases and in many others to a large extent it is reversible. A person with one or both lungs well collapsed by pneumothorax can return to work and to normal function much earlier and can continue relatively strenuous activities much more safely than one who has recovered on rest or phrenic nerve block or pneumoperitoneum.

This is the bright side of pneumothorax. The dark side is provided by the pleurisy which often complicates it. These vary from small asymptomatic accumulations of fluid through acute transient tuberculous infections to tuberculous empyema or mixed infection empyema or most serious of all to empyema with bronchial fistula. The least of these produce some slight thickening of the visceral pleura which does not interfere with eventual complete re-expansion of the lung. The important ones partially compromise re-expansion and the truly serious ones prevent it and lead to the necessity for extensive thoracoplasties, decortications or pneumonectomies. Fortunately, the serious complications are rare and are usually in proportion to the extent of the original dis-

ease Today with the use of antibiotics it is possible to meet and overcome most of the complications without resorting to major surgery

One can say, therefore, that artificial pneumothorax may be used as an elective procedure in minor cases which might occur without it if the temperament of the patient is such that he will not submit to rest or if his economic and social situation demand an early return to a strenuous life. In cases which require major collapse it is the most effective and the least serious and should therefore be tried before attempting major surgery.

In the treatment of a disease as threatening and incapacitating as tuberculosis the slight risks incident to treatment with pneumothorax are worth running. It is important in that it permits young women to marry and have children and young men to proceed with their strenuous careers.

It is difficult to weigh these advantages against the disadvantages and risks. The overconfidence which leads some to use pneumothorax early and indiscriminately and to send the patients back to work without an adequate period of bed rest is not justified nor on the other hand is that attitude justified which is so cautious that it subjects patients to years of unnecessary invalidism and sends them back into life so hampered with restrictions that their lives are spoiled. Certainly pneumothorax is sufficiently safe to be used as an elective procedure to enable individuals to resume normal strenuous careers without too long a period of invalidism.

Some phthisiologists prefer thoracoplasty to artificial pneumothorax. They feel that in the long run it is safer and that strictly unilateral disease extensive enough to require collapse had best be collapsed permanently.

From a statistical point of view this attitude is probably correct. Unfortunately tuberculosis occurs in human beings and most of these greatly prefer the inconveniences and slight risks of pneumothorax with its high chances of success to a permanent loss of ribs and irreversible alteration in the body contour.

THORACOPLASTY AND EXTRAPLEURAL PNEUMONOLYSIS Thoracoplasty and extrapleural

pneumonolysis are the two forms of major surgical collapse. Both are excellent operations. Each has its advantages and disadvantages and its particular uses and indications. Of the two, thoracoplasty is the better operation and should be employed in preference to extrapleural pneumonolysis unless there are definite contraindications.

drastic and even less permanent reduction in vital capacity. As long as the dead space and the foreign body are present they can cause trouble. The late complications which are the only drawbacks of this operation are usually bothersome rather than serious. Late tuberculous or nontuberculous infection in the space which may occur even after many years can usually be cleared up by aspiration and irrigation and perforation of the lung with expectoration of the foreign body can usually be handled by removing the foreign body and performing a local thoracoplasty. The complications are however sufficiently frequent and serious to make thoracoplasty the preferable operation.

The extrapleural operations should be used therefore only when there are definite contraindications to thoracoplasty. These are age, low vital capacity and bilateral involvement which demands or may demand bilateral surgical collapse. The extrapleural operations find their greatest use in older individuals with small chronic apical disease and in those with bilateral symmetrical chronic hematogenous tuberculosis.

MONALDI'S SUCTION DRAINAGE AND CAVITY CLOSURE When Monaldi first reported his method of the suction drainage of tuberculous cavities, most phthisiologists greeted it with a real though guarded enthusiasm. The closure of cavities is the chief problem in the treatment of tuberculosis and this seemed a simple way of solving it. It does close cavities and if the cavities stayed closed the procedure would be the most important and

the most generally applicable of any in the armamentarium. Unfortunately in most instances they reopen soon after the suction is stopped and the catheter withdrawn. Its great uncertainty and the paucity of good permanent results have limited its use to cases in which no other treatment is possible. It should be used therefore only when previous collapse and low vital capacity absolutely contraindicate further collapse or resection or as a preliminary procedure to thoracoplasty for extremely large apical cavities.

In writing of Monaldi's drainage at the present time one must entertain the possibility that the parenteral and intracavitary administration of streptomycin may prove to have increased its effectiveness and widened its indications or that if this has not been done by streptomycin it may soon be done by some new and more effective drug. The method fails only because the tuberculous infection on the opposed surfaces of the cavity prevent healing adequate to resist the forces tending to reopen the excavation. If the infection could be completely overcome the healing would probably be firm and permanent. Maurer of Davos has recently reported good results in the closure of early cavities by Monaldi's drainage used in conjunction with streptomycin. This suggests that the procedure may need to be retried and re-evaluated. Our results have been more permanent since the advent of streptomycin and since on discontinuing the suction we have left the tube in place and continued the drainage indefinitely as a cavernostomy. We have not retried it on early and less resistant excavations.

Cavernostomy has practically the same limitations and the same indications as Monaldi's drainage. Its application with skin flap drainage designed to be permanent is a frank admission of its present inadequacy.

Lobectomy and Pneumonectomy. At the present time lobectomy and pneumonectomy performed for pulmonary tuberculosis are much less safe than the same operations performed for nontuberculous disease. They are also definitely more dangerous than are thoracoplasty and extrapleural pneumonolysis. The dangers are incident to the nature of the tuberculous infection which is rarely limited to one lobe or one lung and which

under general anesthesia spreads easily from one lobe to another. Streptomycin and the use of bronchial intubation have done much to decrease the dangers of spread during the operation. In spite of this at the present time resection is definitely more dangerous than are thoracoplasty or extrapleural pneumonolysis. It seems reasonable therefore to resort to resection only in those cases in which collapse has failed or seems extremely likely to fail.

Resection is indicated in the following conditions:

- (1) Bronchial tuberculosis producing important narrowing of the bronchus
- (2) Extremely large apical cavities
- (3) Basal cavities which do not respond to artificial pneumothorax
- (4) Excavated tuberculomas
- (5) Cavities which remain open after a well performed thoracoplasty

Streptomycin. Prior to the development of streptomycin there was no drug which had an appreciable effect upon the tuberculous infection. Many drugs had been tried and some had been heralded and used but after trial and controversy all had been given up as valueless. It seemed obvious that when a good drug was found its effects would be so unquestionable that it would be immediately acclaimed and generally adopted. This was the case with streptomycin. In the test tube in experimental animals and finally in human beings afflicted with tuberculosis it was immediately demonstrated to have an inhibitory effect upon the growth and increase of the tubercle bacillus and upon the development and spread of the tuberculous infection. When in November 1946 it became available for general clinical use it was immediately adopted and no one then or since has questioned its value.

The universal agreement concerning its effectiveness has not prevailed as to its use. Opinion has differed widely over the type of case in which it is indicated and the dose which should be used. In the beginning it was necessary to proceed with caution. Streptomycin was known to have some unfavorable side effects and no one was sure that other even more serious ones might not become apparent. The drug also was in short supply and was accordingly expensive. There was not enough available to treat every case.

and in public sanatoria there were insufficient funds. For these reasons it was necessary to consider the drug as still experimental and also to select patients to whom it should be given. To satisfy the general clamor for it it was necessary to emphasize the fact that it was not free from danger and also to state dogmatically that although it was helpful it was indicated only in certain types of cases.

In most institutions streptomycin boards were set up to observe the good and bad effects of the drug and to select patients to whom it was to be given. The clinical necessity for caution and the economic necessity for distributing a limited supply subtly affected the clinical judgment of the members of the boards both as to dosage and indications with the result that even after the drug in certain doses had been proved not to be dangerous they continued and still continue to insist that it is valuable but should be used only in certain types of cases. One can not escape the suspicion that what they said so often from clinical caution and economic necessity they have now come to believe. And in this line it seems quite certain that the dosage will increase the course of treatment lengthen and the indications widen as the price of the drug decreases.

The reasons given for the selection of cases are as follows:

(1) Streptomycin is of value only in soft exudative lesions; it is not effective in chronic fibroid lesions.

(2) In far advanced and hopeless cases it cannot possibly bring about arrest of the disease.

(3) In minimal, easily controllable and moderately advanced lesions streptomycin is not necessary and should not be used because it renders the bacilli immune to the drug and will make the drug useless should the disease progress or recur and become more serious.

The first reason would be valid if it were true in type or if any phthisiologist could classify each case exactly. It has been our experience that streptomycin is valuable in chronic tuberculosis that every chronic case has some acute exudative elements and that the rather pernicious type of clinico-phthisio-pathologist roentgenologist who can look at a roent-

genogram and describe the exact type of lesion present—as if he had made a personal tour of the trachea, bronchi and alveoli and on the basis of this minute knowledge can tell whether or not streptomycin will be effective—is likely to be wrong. The results which can be expected from streptomycin are predictable only within limits. Anyone who uses it extensively is being continually surprised by unexpected results and therefore will have to conclude that a certain a priori judgment is impossible. One cannot say "Streptomycin will or will not help this case." Only after having used it in that particular case can he say "Streptomycin did or did not benefit it" and even this statement is often uncertain.

To refuse to give streptomycin because a case is so far advanced that recovery cannot possibly be accomplished is to assume too much prognostic ability. One of the great roles of streptomycin is that of bringing apparently hopeless cases back into the curable group. At the Edward Sanatorium before the advent of streptomycin there were approximately 25 deaths each year. Since November 1946 this number has been reduced to 7 and this reduction has been chiefly in the group which formerly would have been considered hopeless.

To say that streptomycin should not be used for minimal and easily controllable moderately advanced lesions because it renders the bacilli immune to the drug and therefore precludes its use should the disease progress or recur is not reasonable. In this group if treatment is adequate the normal recovery rate is approximately 90 per cent. With streptomycin it will certainly be higher and the period of rest and the necessity for collapse will be reduced. Furthermore it has been our experience that bacilli resistant to a small dose of streptomycin are not resistant to larger doses. In less urgent cases the dose should be small enough to obviate any risk of eighth nerve injury and it should be stopped immediately if untoward symptoms appear. All things considered it seems best to use the drug in these cases because of the increase in security which it affords and to count on larger doses and the old methods of treatment in the few cases in which the disease recurs.

Those who advocate the selection of cases

have overlooked the great importance of

testinal and other forms of extrapulmonary tuberculosis. This is one of its major functions. These complications, which formerly were prevalent and accountable for many deaths, are now rare. If it had no effect upon existing lesions, it would still always be indicated merely to prevent the development of new ones.

COMPLICATIONS OF STREPTOMYCIN THERAPY. Streptomycin has been used too short a time to permit one to say that all of its complications have been noted. Thus far the only serious complication has been permanent injury to the vestibular apparatus and its resultant loss of a sense of equilibrium. The original dose of 2 gm. a day of the old streptomycin produced temporary dizziness in many patients and permanent dizziness in a few. Most of those with permanent eighth nerve damage adjusted well to the loss. They developed new ways of maintaining balance and were inconvenienced only when in the dark. This readjustment was most rapid and complete in young individuals, less rapid and less complete in older ones. In general the

nerve is in part a matter of individual sus

and on the rate of excretion. Excretion is largely by the kidneys and for this reason extra care in using it is indicated in older individuals and in those with impaired renal function. If any kidney damage is suspected and it should be expected in old people, renal function tests should be run before administration of the drug and the dose should be regulated according to the results of these and should be checked by determinations of blood concentration. If facilities for testing the blood concentration are not available, it is sufficient to watch carefully for complications and to stop the drug or reduce the dose if they appear.

Permanent impairment of the sense of equilibrium is nearly always well compensated. It is an inconvenience rather than a

serious and disabling handicap. It is a small price to pay for recovery from military tuberculosis or from severe forms of chronic phthisis. Any important risk is not worth running in minimal tuberculosis or in the milder forms which are nearly certain to recover without it. This statement should not be interpreted as meaning that the drug should not be used in these cases, merely that it should be used in such doses that complications will not develop and that it should be stopped if any do appear.

Doses of 0.5 to 1 gm. of old streptomycin varied according to body weight and renal function rarely produce any damage to the eighth nerve. Dihydrostreptomycin, which has only recently appeared on the market, appears to be much less toxic so that doses of 2, 3 or even 4 gm. a day can be used without danger of nerve injury. It is too

not develop suddenly and that if the drug is

the proper dose of streptomycin or the proper interval between doses. Opinion on these matters has been somewhat influenced by the

be in proportion to the concentration of the drug that reaches them. It is known that different strains of the organism vary in their susceptibility to the drug and that all strains acquire resistance to it. We have noted that some cases which fail to improve on 1 gm., improve rapidly when the dose is raised to

There is so much to be learned on the whole subject that at the present time and for some time to come, an expectant open-mindedness should be the proper attitude. It may be that large doses for a short time are preferable to smaller doses for a long time etc. It seems certain that the important factor is the concentration in the blood and the dose should be adjusted to the body weight and to the rate of excretion by the kidneys.

No one yet knows how to fit streptomycin into the old formulas of treatment. Over many years phthisiologists have learned by experience how much bed rest is required to arrest certain types of cases and what can be expected from rest and from the various forms of major and minor collapse. They have developed formulas for the management of different types of cases. These formulas have now been completely upset by the introduction on one side of the equation of an unknown factor. They knew for instance that in minimal tuberculosis the formula was

Bed rest (6 months) plus partial rest (6 months) = cure. Now with streptomycin added the formula is

Bed rest (? months) plus partial rest (? months) = cure. It will require many years and long clinical experimentation to answer these questions. But at the present time one is safe in assuming that streptomycin has not changed the treatment of tuberculosis. It has merely strengthened a treatment which has always been inadequate and uncertain. One should continue to use the old formulas and to consider streptomycin an adjunct which will make success more common.

Thus far one can conclude

- (1) Streptomycin is almost a specific remedy for miliary tuberculosis and for intestinal, laryngeal and vesical tuberculosis.
- (2) In acute and chronic tuberculosis it has an important favorable effect obviating the necessity for collapse in milder cases and bringing many far advanced cases back into the group in which collapse can be used.
- (3) It greatly reduces the incidence of hemorrhage and sudden spread of the disease to new lung areas and also of the extra pulmonary complications of tuberculosis.
- (4) It renders spreads during surgery and general anesthesia much less common.
- (5) All in all it has greatly reduced the death rate from tuberculosis.
- (6) Used with care and in proper dosage it has no serious complications. What complications it has are less important than the dangers of serious tuberculosis and can be avoided in cases which might recover without it.
- (7) It should therefore be used in all cases.

The Types of Pulmonary Tuberculosis and Their Treatment. Pulmonary tuberculosis is not a single disease. The tubercle bacilli reach the lungs by various routes and the forms of disease caused by each type of pathogenesis differ profoundly. The basic distinction is between the hematogenous and the bronchogenous routes of infection. Within the hematogenous group the route is probably always the same, the disease

the resistance of the individual and the virulence of the organisms. Clinically the disease varies from acute miliary tuberculosis to the most chronic and smoldering types of phthisis. It may be classified as follows:

- (1) Acute progressive miliary tuberculosis
- (2) Cold miliary tuberculosis, the French *tuberculose miliaire froide*
- (3) Chronic hematogenous tuberculosis
 - (a) early subacute stage
 - (b) middle chronic stage
 - (c) late chronic stage

MILIARY TUBERCULOSIS. The clinical picture and course of acute miliary tuberculosis are well known. The source of the infection is an active tuberculous lesion, either in the thoracic duct or some blood vessel which continuously feeds large numbers of bacilli into the blood stream. This may involve many organs or chiefly the lungs or one lung or only the meninges or the liver. The disease is practically always steadily progressive and fatal, the infection extending past its original site to involve many organs and eventually the meninges.

Before the discovery of streptomycin there was no effective treatment. Streptomycin will cure most cases if it is used before the meninges become involved. The dosage should be large and the course prolonged. It should be combined with a long period (6 months to one year) of complete bed rest after the

made to make an early diagnosis and to start treatment at the inception of the disease.

Cold miliary tuberculosis has the same

pathogenesis and the same roentgenologic picture as acute progressive miliary tuberculosis. Just why the symptomatology and course are so different is uncertain. There is little or no fever, slight cough and no dyspnea. Response to simple rest in bed is often good; the lesions in the lungs often clearing completely. There is the same danger of meningitis and also of the development of localized infections in other organs. The treatment is administration of streptomycin and rest as in progressive miliary tuberculosis.

CHRONIC HEMATOGENOUS TUBERCULOSIS
Subacute and chronic hematogenous pulmonary tuberculosis is a distinct and important type of chronic phthisis differing profoundly from the bronchiogenic type in its symptoms, its course and in the indications for treatment. It is poorly understood even by many phthisiologists; is often con-

focus in a lymph node adjacent to a blood vessel which sends occasional showers of bacilli into the blood stream.

It is an extremely slow creeping infection which progresses insidiously over many years producing few or no symptoms either local or general until it is far advanced. In all save its late stages the pulmonary and systemic symptoms and signs are so slight that when by chance it is found on the roentgenogram it is often considered to be a healed lesion. For the same reasons the first important symptoms are often those of some extrapulmonary complication such as laryngitis, enteritis, fistula in nose or some focus of skeletal tuberculosis. Cases are thus often referred to the phthisiologist by the laryngologist, the urologist, the proctologist or the orthopedic surgeon.

It is usually symmetrically bilateral and apical although it may occasionally be unilateral or even basal. In its early stages it shows on the roentgenogram as coarse miliary seedings usually in both apices. Over the course of years it extends gradually downward until all or both lungs may be involved. The older, denser and more fibrotic lesions are in the apices. Eventually excavation occurs. The cavities are thin walled and therefore difficult to distinguish. They are

usually in the upper lung areas and in both lungs.

The involvement develops over many years so that the disease becomes clinical only in the third, fourth or fifth decade of life. Except in the late stages cough is slight and expectoration scanty. Bacilli are usually hard to find and are often discoverable only by guinea pig inoculation. Extrapulmonary complications are common. Occasionally the

both
n the

early stages treatment scarcely seems indicated and in all save the extremely late stages response to treatment is extremely rapid and misleadingly satisfactory. After a few weeks or months in bed rapid gain in weight and the disappearance of all signs and symptoms even of bacilli from the sputum convince the patient and too often the physician that arrest has been accomplished. For these reasons most cases are undertreated. They return to work and then back to the sanatorium again and again each time with more advanced disease until finally they no longer respond to treatment and are no longer curable.

This type of tuberculosis requires prolonged rest in bed and often either unilateral or bilateral collapse. Streptomycin should the
por
n in

far advanced and chronic cases. Experience with streptomycin and pneumothorax indicates that safe healing has been accomplished only when the lesions have either disappeared or are well collapsed.

In the bilateral cases and most cases are bilateral a course of streptomycin and 6 to 8 months of rest in bed will usually clear all save the older and more fibrotic lesions in the apices. At this point collapse must be considered. It can safely be omitted only if nearly all of the lesions have resolved and all cavities have closed. Small residual cavities are particularly difficult to recognize by any means save fluorography. If cavities persist collapse must be used. Artificial pneumothorax or extrapleural pneumonolysis are the procedures of choice. Because the disease is usually bilateral thoracoplasty is rarely indicated and bilateral intrapleural or

extrapleural pneumothorax are often demanded. Phrenic nerve block on the worse side, alone or with pneumoperitoneum, may be used early.

BRONCHIOGENIC TUBERCULOSIS. Bronchiogenic tuberculosis differs from chronic hematogenous tuberculosis in almost every characteristic. Whereas the latter is usually smoldering and steadily and slowly progressive, the bronchiogenic form is often flaming and febrile, progressing early to caseation and excavation and traveling from lobe to lobe and lung to lung by a series of relatively closely spaced acute incidents. Hematogenous tuberculosis is usually bilateral, but the bronchiogenic type in its early stages is nearly always unilateral, becoming bilateral not by its nature but as the result of an accidental spill of bacilli into the unaffected lung. While hematogenous tuberculosis is primarily a disease of the middle decades of life, the bronchiogenic type affects chiefly young adults and occasionally older people whose resistance has diminished. With this form, extrapulmonary complications are rare, with hematogenous tuberculosis they are common.

Within its own category, bronchiogenic tuberculosis varies tremendously, the variations depending on the pathogenesis, the number of bacilli which establish the infection, the stage of the disease and also the variable relationship between the allergy and resistance of the individual and the virulence of the organism. It is a striking fact that in any individual recurrences or spreads of the disease follow a pattern peculiar to that person. The picture of the disease varies from the symptomless early infiltrate or the purely bronchial irritation of a perforating lymph node, through acute bronchopneumonia or lobar pneumonia on through all stages of extent and chronicity, from progressive and rapidly fatal widespread caseation to a chronic, almost asymptomatic, fibroid tuberculosis.

The pathogenesis of reinfection bronchiogenic tuberculosis is either exogenous or endogenous, i. e., the bacilli either reach the lung directly by inhalation from some source outside the body or are disseminated in the air passages from some part of the primary complex, either from the focus in the lung or from a hilar lymph node. In exogenous

reinfection the mechanism is single and obvious, in endogenous reinfection it is various.

THE PROGRESSIVE PRIMARY INFECTION. Now that the primary infection is so often postponed past the highly resistant period of childhood and into puberty and adulthood

into phthisis. This may occur as the result of excavation and extension of the lung focus but more frequently from rupture of the enlarged hilar lymph nodes into the lung or into a lobar bronchus. The marked involvement of these glands is the chief characteristic of primary tuberculosis and is what makes the progressive primary infection different clinically from late reinfections. The enlarged nodes often press upon the bronchus narrowing it and producing a wheeze and later an atelectasis. Cough, wheeze, and perforation with positive sputum may occur before there is any obvious parenchymal involvement or the first evidence of the disease may be a massive tuberculous pneumonia from sudden rupture of a caseous and purulent gland into the bronchus. The spilling of bacilli may, however, be slight, producing only a little bronchopneumonia or even only one or more infiltrates.

It is important to recognize this type of lesion, as it is the one most often leading to severe bronchial tuberculosis and to stenosis. The explosive cough often threatens spread to other lung areas. Use of streptomycin is imperative and early collapse or even excision may be indicated. Light doses of roentgen rays over the hilar region may

many tuberculosis are usually reflected the parenchyma must be reversed to primary infection tubercle bacilli remain active

in the elements of the complex. Late reactivation of the primary pulmonary focus is rare but reinfection from reactivated hilar lymph nodes is common. These too may cause severe bronchial tuberculosis and bronchial stenosis and atelectasis.

Onset and course of the disease depend on the dosage of bacilli and the reaction of the individual. The sudden rupture of a caseous lung or gland focus produces an extensive bronchopneumonia or lobar pneumonia while the aspiration of a few bacilli as in exogenous reinfection produces a tiny area of bronchopneumonia with few or no symptoms and soon rounds up into an "early infiltrate." The severity of the reaction, the amount of perifocal exudate and the tendency to caseation, excavation and progression all depend on the allergy and resistance of the particular patient and probably also on the virulence of the offending organisms. In some resolution and clearing occur without caseation and excavation and in others these processes are rapid and extensive. In each case every recurrence and spread tend to follow the pattern of the original lesion.

Progress and extension of bronchogenic tuberculosis are rarely steadily progressive. They occur usually by a series of acute incidents as bacilli are aspirated into new pulmonary areas. These extensions may be

treatment. More often it becomes caseous and breaks into the air passages leaving a cavity at its site and producing a contiguous area of bronchopneumonia. From this point on when the sputum has become frankly positive and excavation has occurred all cases of bronchogenic tuberculosis are roughly similar. Progression from lobe to lobe and from lung to lung by aspiration of bacilli is the rule.

We have then the following types of pulmonary tuberculosis:

- (1) Hematogenous tuberculosis
 - (a) acute miliary
 - (b) subacute miliary
 - (c) chronic hematogenous

- (2) Bronchogenic tuberculosis
 - (a) the primary complex
 - (b) the progressive primary complex
 - (c) late autogenous reinfection
 - (d) exogenous reinfection

Reinfection. The Treatment of Types of Bronchogenous Tuberculosis. THE EARLY INFILTRATE. The early infiltrate is a round sharply delimited focus is the earliest demonstrable form of bronchogenous tuberculosis. It is the result of a small area of bronchopneumonia caused by the aspiration either from an exogenous or an endogenous source of a small number of tubercle bacilli. It may cause fatigue or even hemoptysis but is usually asymptomatic. It is of tremendous importance because it is the breeding ground for large numbers of bacilli which may escape either gradually or suddenly to infect other lung areas and produce widespread clinical tuberculosis. It may heal without treatment but usually in young adults and too frequently in all age groups the center of the infiltrate caseates, liquefies and finally breaks through to discharge large numbers of bacilli into the surrounding lung. The larger it is the more likely is it to do this and the less likely is it to heal by conservative treatment (see tuberculoma).

Such a lesion found on a routine roentgenogram poses an important diagnostic problem. It must be distinguished from the pulmonary focus of primary tuberculosis from coccidioidomycosis from a benign or malignant tumor and from an old healed lesion. In every instance the physician must decide whether it is tuberculosis and if so whether it is active and dangerous or old and safe.

Since some infiltrates will heal with no treatment no one can tell how little treatment is needed in any given case. He must aim therefore to give that amount of treatment which will produce a cure in practically 100 per cent of cases.

Before the advent of streptomycin one could feel safe in prescribing 6 months of bed rest and 6 months of graduated exercise. If streptomycin is used these periods can probably be shortened but at the present time no one knows to what extent. One would be justified in trying a series of cases on 3 months of bed rest and 3 months of limited activity.

Many physiologists feel that streptomycin

should not be used in minimal tuberculosis. They maintain that it is not needed and that it is unwise to render the bacilli resistant and so decrease the effectiveness of the drug should the infection recur or spread. This danger is more imaginary than real. If the cases are properly handled 90 to 100 per cent should remain well and should the disease recur larger doses of streptomycin could be used and other more radical methods of treatment.

Some clinicians use phrenic nerve block combined with shortened periods of bed rest and inactivity.

Artificial pneumothorax is a good safe and sure method of treatment. It is indicated when there is need for an early return to work or where the normal life of the individual is certain to be strenuous. It should be preceded by a few months of bed rest.

TUBERCULOMAS. Infiltrates vary in size and their tendency to central liquefaction and evacuation is greater in the larger lesions. These larger infiltrates are called tuberculomas. Some of them do heal completely and remain in the lung as annular opacities which are with difficulty distinguished from benign or malignant tumors. Those that do not heal persist as thick walled cavities which because of the thickness of their walls rarely close spontaneously and are difficult to close by collapse measures. They may appear to close and heal but often this means only that they have become filled with inspissated secretions which will again liquefy and be evacuated.

Active or recurrently active tuberculomas are often an indication for lobectomy or partial lobectomy. This does not mean that all large infiltrates should be immediately excised. In tuberculosis there is no rule or indication that is universal. Many of them do heal on simple bed rest and streptomycin or on pneumothorax. These measures should be tried first and resection reserved for those that do not respond or appear unlikely to respond to the simpler treatment.

THE EARLY INFRACLAVICULAR CAVITY WITH BRONCHOPNEUMONIA. This is the classical picture of early bronchogenous tuberculosis. Although the early infiltrate may occur any place in the lung from the extreme apex to the base it is most common in the posterior portion of the upper lobe at a level which

on the usual roentgenogram places it in the *infraclavicular* region. When an infiltrate evacuates it most often does so quite suddenly spilling secretions rich in tubercle bacilli into the surrounding lung area and producing quickly a cavity surrounded with a greater or lesser amount of bronchopneumonia.

When such a lesion first develops it is what is called "hot." This means that there is still an active and acute tissue reaction and that about each focus of tuberculosis there is an area of perifocal exudate. Any active interference at this stage is apt to do more harm than good. Artificial pneumothorax is almost invariably followed by an acute pleurisy and the collapsed pneumonic areas often undergo organization and fibrosis rather than resolution. The patient should be put on absolute bed rest and streptomycin.

Before the advent of streptomycin such contralateral spread was common even while the patient was under treatment and the disease these

of the exudate and decrease in the size of the cavity are almost the rule. After a preliminary period of bed rest and streptomycin phrenic nerve block or this and pneumoperitoneum may reasonably be employed. One hopes that the lesion will clear and the cavity close without further interference. Cavity closure is the great question and the great problem and the use of these essentially benign procedures during the period when the lesion is most labile certainly favors the closure of the cavity and so may do much to obviate the necessity for subsequent major surgery.

If pneumothorax is to be used either as a procedure necessary for the closure of cavities or as one of choice to hasten and make certain of recovery it had best be postponed until nearly maximal benefit has been obtained from bed rest. The smaller the cavity and the more quiescent the disease the more likely is pneumothorax to be successful and uncomplicated.

Major surgery thoracoplasty should be resorted to only when all other measures have proved unsuccessful.

In this type of unilateral or predominantly unilateral disease there is a tendency to overlook or ignore small lesions in the opposite lung. An infiltrate or a small area of involvement seems little in comparison to the predominant lesion. If a little focus in the opposite lung were all of the disease, one could take it seriously and treat it by prolonged rest or pneumothorax. Actually one has a tendency to forget it and where collapse is used early on the worse side to permit too early activity. Many of the recurrences following successful pneumothorax develop from small lesions in the opposite lung which have been neglected. When one treats tuberculosis on the basis that it is unilateral he must be sure that it is truly unilateral.

LARGE APICAL CAVITIES Extremely large cavities in the apex of the lung are not readily closed by pneumothorax or even by thoracoplasty. Many of these are tension balloon cavities in which air is entrapped under pressure. This prevents collapse. Others are simply too large to have their walls approximated by the amount of collapse which a thoracoplasty can provide. Many of these will so decrease in size on bed rest and streptomycin that thoracoplasty can eventually be used.

If they remain large they can be handled in one of two ways either by excision or by Monaldi's suction followed by thoracoplasty.

CAVITIES IN THE APEX OF THE LOWER LOBE Most cavities which appear close to the hilus are in reality posterior to the hilus in the apex of the lower lobe. Bed rest, streptomycin and phrenic nerve block are almost specific for cavities in this location. In most instances they close rapidly and completely. Pneumoperitoneum may also be used.

If such a cavity persists in spite of conservative treatment pneumothorax should be tried. If this is unsuccessful excision is the procedure of choice. Thoracoplasty is rarely effective.

CAVITIES IN THE LOWER PORTIONS OF THE LOWER LOBE In contrast to cavities in the apex of the lower lobe which are easy to close, those in the base are extremely resistant. Phrenic nerve block and pneumoperitoneum which theoretically should be most effective usually merely raise them higher in

the chest. If these will not close with pneumothorax lobectomy is indicated.

BILATERAL BRONCHIOGENIC TUBERCULOSIS In bronchiogenic tuberculosis the disease has always started in one lobe of one lung and has spread from there into other lobes and into the opposite lung by a series of spills. For this reason one lung usually is more extensively involved than the other and the lesions in the opposite lung may vary from minimal infiltrations to far advanced disease with cavitation.

Minimal and moderately advanced disease in the opposite lung will heal on bed rest and streptomycin so that the lung more seriously affected may eventually be handled as if the disease were truly unilateral. If however the disease is more extensive the problem is much more difficult. One must then take full advantage of every form of treatment.

Nearly every such case should be kept on bed rest and streptomycin and perhaps pneumoperitoneum until maximal benefit has been obtained from these procedures. Direct collapse should be started only when progress has stopped (4 to 8 months) or when hemorrhage or severe cough threatens spread of the disease or extension does actually take place. One must aim always to arrest the disease in the lung less seriously involved so that surgical collapse may be used on the opposite side. Bilateral pneumothorax may be successful but often it is necessary to use pneumothorax on the better lung as a preparation for thoracoplasty on the opposite one. If this is successful it is the easiest way out. If it is impossible, one may have to use one of many combinations of bilateral surgical treatment i.e. bilateral paraffin packs or prick on one side and thoracoplasty on the other or thoracoplasty or prick on one side and Monaldi's suction or cavernostomy on the other. In such cases one must choose from his armamentarium and mix and combine the procedures to meet the particular situation in each lung area.

Bronchial Tuberculosis Tuberculosis of the bronchi is relatively common and is one of the most important of the complications of pulmonary tuberculosis. It may develop either as the result of implantation of the mucous membrane or by direct extension from the hilar lymph nodes. These may com-

press erode or perforate the bronchus during the primary infection or much later latent and apparently healed infection in them may become exacerbated and do the same things

Involvement of a bronchus becomes important only when it causes bronchial narrowing. When this occurs the lobe or lung does not drain well and the tuberculosis in it tends to remain active. Cough is often or usually severe and explosive and the narrowed bronchus acts as an atomizer through which infected secretions are sprayed widely to other lung areas. If the bronchus becomes extremely narrow plugs of mucus frequently block it completely causing a retention of secretions and an elevation of temperature. When the plug is finally coughed out production of sputum recommences and the temperature falls. If the bronchus becomes completely stenosed by scar tissue the lung distal to it may heal in complete atelectasis. This is a rare termination and is not to be expected.

Small implantation ulcers in the bronchus are common and not of great significance. They usually heal as the pulmonary lesions heal or are collapsed. It seems probable that most important bronchial tuberculosis develops by extension from peribronchial lymph nodes and that in these instances the bronchial perforation is the cause of the pulmonary infection. This is suggested by the clinical observation that most cases of serious bronchial obstruction commence with the symptom of wheezing and that the picture of bronchial stenosis is present from the onset. It is further suggested by the fact that one occasionally sees cases of bronchial tuberculosis which have not yet developed parenchymal lesions. If these are watched pulmonary tuberculosis eventually develops and often with the sudden onset of atelectasis.

This mechanism is common in primary tuberculosis in which glandular involvement predominates. It can also develop late from exacerbations in quiescent glands. In these days when the primary infection is so often delayed until an age when resistance to tuberculosis has fallen off it seems probable that many of the cases of severe bronchial tuberculosis are the result of such a progression from a first infection.

The immediate threat from bronchial tuberculosis is in proportion to the severity of the cough. In some acute cases this is so extreme that wide dissemination from what at first seems a small and relatively unimportant lesion is rapid.

The treatment of bronchial tuberculosis with stenosis is usually excision. Cases vary so greatly and respond so variously to other forms of treatment that no hard and fast rule can be laid down. There is a tendency to be conservative and usually conservatism is poorly rewarded. By observing the nature of the lesion the severity of the cough and the amount of sputum one can tell in which cases delay and the trial of other methods are safe. The great danger is spread to the opposite lung.

The early hope that streptomycin would be as effective in this type of tuberculosis as in that of the larynx has not been fulfilled. It will usually cure small implantation ulcers but is only temporarily successful in the severe forms.

When the narrowing is caused by the acutely enlarged glands of a progressive primary lesion streptomycin and the natural course of the disease in which these subside and contract will frequently result in opening of the bronchus and clearing of the tuberculosis.

Cauterization of the ulcers with 10 per cent silver nitrate solution is sometimes effective and should always be tried.

Pneumothorax is usually effective temporarily and sometimes permanently. By cutting down the cough it lessens the danger of spread and by decreasing the flow of bacilli over the affected bronchus it favors healing. The immediate good results are often misleading and it should be used and persisted in only in cases in which there are definite contraindications to thoracoplasty and excision.

Thoracoplasty may well be tried before excision. It will frequently produce a satisfactory result but if wheeze, positive sputum or "damming" spells continue lobectomy or

as a complication of obvious parenchymal lesions or may occur as an apparently independent disease. In the latter case one must

assume that the lung is minimally involved. In both cases treatment must be directed chiefly toward cure or prevention of the pulmonary tuberculosis.

In nearly every instance the pleurisy itself is a relatively benign self-limited disease. The fever subsides and the fluid resorbs over a period of several weeks. If the outpouring of fluid is so excessive as to produce dyspnea

pleura will become so thickened (even calcified) that the lung will be prevented from re-expanding. In most cases aspiration is neither necessary nor advisable.

Some phthisiologists have advised converting the pleurisy into a pneumothorax and continuing the collapse for a year or two in order to prevent development of tuberculosis in the lung. This means that the pneumothorax at its initiation is complicated by an acute pleurisy and therefore that the pleura will become thickened and re-expansion difficult. The procedure seems indicated only if there are lesions in the lung which appear definitely to need collapse.

The great danger of idiopathic tuberculous pleurisy with effusion is the subsequent development of pulmonary tuberculosis. This may occur a few months or many years after the acute disease and in spite of the fact that at the time of the pleurisy the lung appears free of disease. It is estimated that between 35 and 45 per cent of cases later develop consumption unless they are treated for consumption at the time of the pleurisy.

Every patient should be treated as if he already had a minimal pulmonary tuberculosis. This means that he should have approximately 6 months of bed rest in a sanatorium and a further 6 months period of partial rest at home. Following this he should be checked by periodic roentgen ray examinations for the remainder of his life.

Streptomycin in small doses may be used during the acute stage of the disease.

The Patient in the Treatment of Pulmonary Tuberculosis. We have spoken thus far of the methods of treatment and the types of tuberculosis. It remains to say something concerning the patient as a human being who has psychologic, social and economic problems peculiar to himself. To an impor-

tantologist must be to make tuberculosis an incident in the normal life of the patient rather than an altering and revolutionizing disaster. He should assume that his function is to return the patient as soon as possible to his home and to his former career and occupation or at least to a career and occupation which are normal for an individual of his age and abilities. The old idea should be abandoned that a bout with tuberculosis forbids forever hard work, marriage, childbearing or any normal activity as should the new idea that it should be made the occasion for months and years of re-education and rehabilitation. The phthisiologist should consider himself as a curer of a disease rather than as a re-educator or a meddler in the normal lives of his patients.

One can say definitely that that person recovers best who recovers with the least mechanical interference or with that which is the least drastic and the least subject to complications. But one knows also that collapse of a lung by pneumothorax or even thoracoplasty will greatly hasten recovery and will greatly lessen the chances of recurrence and will permit a more strenuous life. On this basis one will treat one case of minimal tuberculosis with 6 months in bed and 6 months of restricted life, another with 3 months in bed and pneumothorax still in other with immediate pneumothorax and return to work after a few weeks. Young people who are naturally energetic and active and who must and should be so if they are to establish a position in life probably should all have pneumothorax. This is particularly true of medical students, interns and residents, mothers with small children or young women who should have children in the near future.

In all of this one must steer a middle course governing his procedure by what he thinks is the patient's need and not being influenced by the patient's preference. He will be under constant strong pressure to cut corners, to omit sanatorium care, to shorten bed rest, to proceed early to collapse, to delay collapse too long, etc. etc. He must resist all of this and firmly and yet at the

press, erode, or perforate the bronchus during the primary infection, or, much later, latent and apparently healed infection in them may become exacerbated and do the same things.

Involvement of a bronchus becomes important only when it causes bronchial narrowing. When this occurs, the lobe or lung does not drain well and the tuberculosis in it tends to remain active. Cough is often or usually severe and explosive, and the narrowed bronchus acts as an atomizer through which infected secretions are sprayed widely to other lung areas. If the bronchus becomes extremely narrow, plugs of mucus frequently block it completely, causing a retention of secretions and an elevation of temperature. When the plug is finally coughed out, production of sputum recommences and the temperature falls. If the bronchus becomes completely stenosed by scar tissue, the lung distal to it may heal in complete atelectasis. This is a rare termination and is not to be expected.

Small implantation ulcers in the bronchus are common and not of great significance. They usually heal as the pulmonary lesions heal or are collapsed. It seems probable that

bronchial perforation is the cause of the pulmonary infection. This is suggested by the clinical observation that most cases of serious bronchial obstruction commence with the symptom of wheezing and that the picture of bronchial stenosis is present from the onset. It is further suggested by the fact that one occasionally sees cases of bronchial tuberculosis which have not yet developed parenchymal lesions. If these are watched, pulmonary tuberculosis eventually develops and often with the sudden onset of atelectasis.

This mechanism is common in primary tuberculosis in which glandular involvement predominates. It can also develop late from exacerbations in quiescent glands. In these days, when the primary infection is so often delayed until an age when resistance to tuberculosis has fallen off, it seems probable that many of the cases of severe bronchial tuberculosis are the result of such a progression from a first infection.

The immediate threat from bronchial tuberculosis is in proportion to the severity of the cough. In some acute cases this is so extreme that wide dissemination, from what at first seems a small and relatively unimportant lesion, is rapid.

The treatment of bronchial tuberculosis with stenosis is usually excision. Cases vary so greatly and respond so variously to other forms of treatment that no hard and fast rule can be laid down. There is a tendency to be conservative and usually conservatism is poorly rewarded. By observing the nature of the lesion, the severity of the cough and the amount of sputum one can tell in which cases delay and the trial of other methods are safe. The great danger is spread to the opposite lung.

The early hope that streptomycin would be as effective in this type of tuberculosis as in that of the larynx has not been fulfilled. It will usually cure small implantation ulcers but is only temporarily successful in the severe forms.

When the narrowing is caused by the acutely enlarged glands of a progressive primary lesion, streptomycin, and the natural course of the disease in which these subside and contract, will frequently result in re-opening of the bronchus and clearing of the tuberculosis.

Cauterization of the ulcers with 10 per cent silver nitrate solution is sometimes effective and should always be tried.

Pneumothorax is usually effective temporarily and sometimes permanently. By cutting down the cough, it lessens the danger of spread and by decreasing the flow of bacilli over the affected bronchus it favors healing. The immediate good results are often misleading and it should be used and persisted in only in cases in which there are definite contraindications to thoracoplasty and excision.

Thoracoplasty may well be tried before excision. It will frequently produce a satis-

as a complication of obvious parenchymal lesions or may occur as an apparently independent disease. In the latter case one must

assume that the lung is minimally involved In both cases treatment must be directed chiefly toward cure or prevention of the pulmonary tuberculosis

In nearly every instance the pleurisy itself is a relatively benign self limited disease The fever subsides and the fluid resorbs over a period of several weeks If the outpouring of fluid is so excessive as to produce dyspnea

pleura will become so thickened (even calcified) that the lung will be prevented from re expanding In most cases aspiration is neither necessary nor advisable

Some phthisiologists have advised converting the pleurisy into a pneumothorax and continuing the collapse for a year or two in order to prevent development of tuberculosis in the lung This means that the pneumothorax at its initiation is complicated by an acute pleurisy and therefore that the pleura will become thickened and re expansion difficult The procedure seems indicated only if there are lesions in the lung which appear definitely to need collapse

The great danger of idiopathic tuberculous pleurisy with effusion is the subsequent development of pulmonary tuberculosis This may occur a few months or many years after the acute disease and in spite of the fact that at the time of the pleurisy the lung appears free of disease It is estimated that between 35 and 45 per cent of cases later develop consumption unless they are treated for consumption at the time of the pleurisy

Every patient should be treated as if he already had a minimal pulmonary tuberculosis This means that he should have approximately 6 months of bed rest in a sanatorium and a further 3 months period of partial rest at home Following this he should be checked by periodic roentgen ray examinations for the remainder of his life

Streptomycin in small doses may be used during the acute stage of the disease

The Patient in the Treatment of Pulmonary Tuberculosis We have spoken thus far of the

of the con who has psychologic social and economic problems peculiar to himself To an impor

cure In every instance the aim of the phthisiologist must be to make tuberculosis an incident in the normal life of the patient rather than an altering and revolutionizing disaster He should assume that his function is to return the patient as soon as possible to his home and to his former career and occupation or at least to a career and occupation which are normal for an individual of his age and abilities The old idea should be abandoned that a bout with tuberculosis forbids forever hard work marriage childbearing or any normal activity as should the new idea that it should be made the occasion for months and years of re education and rehabilitation The phthisiologist should consider himself as a curer of a disease rather than as a re educator or a meddler in the normal lives of his patients

One can say definitely that that person recovers best who recovers with the least mechanical interference or with that which is the least drastic and the least subject to complications But one knows also that collapse of a lung by pneumothorax or even thoracoplasty will greatly hasten recovery will greatly lessen the chances of recurrence and will permit a more strenuous life On this basis one will treat one case of minimal tuberculosis with 6 months in bed and 3 months of restricted life another with 3 months in bed and pneumothorax still another with immediate pneumothorax and return to work after a few weeks Young people who are naturally energetic and active and who must and should be so if they are to establish a position in life probably should all have pneumothorax This is particularly true of medical students interns and residents mothers with small children or young women who should have children in the near future

In all of this one must steer a middle course governing his procedure by what he thinks is the patient's need and not being influenced by the patient's preference He will be under constant strong pressure to cut corners to omit sanatorium care to shorten bed rest to proceed early to collapse to delay collapse too long etc etc He must resist all of this and firmly and yet at the

same time must make all reasonable and safe allowances for the patient's peculiar necessity

The physician's first task is that of a persuader or convincer. The treatment for tuberculosis is bitter to take and this bitterness is usually out of all proportion to the symptoms and the sense of illness. When a well or relatively well person is told that he has tuberculosis and must leave his home and work and go to a sanatorium often his first reaction is to refuse to believe the diagnosis and then to say that he cannot or will not follow the advice. The mother cannot leave her home and children or the husband his job. This reaction is natural, is a transient hysteria which should not be taken seriously and is almost the rule. It is moreover a crucial period in the treatment. If the physician fails here he has failed completely and an hour or two spent in convincing the patient of the necessity and feasibility of the treatment is better used than an equal amount of time spent later in performing a thoracoplasty. Throughout the course of treatment tact, understanding and persuasion in holding the patient to the difficult regimen are constantly required. If the patient does not accept treatment or abandons it before it is completed this is the doctor's fault and not the patient's. He cannot say "take it or leave it." He must persuade the patient to take it and any sanatorium physician who has a large number of patients who insist on leaving against medical advice is not a good physician regardless of his knowledge of indications or his skill in technique.

The time element in the treatment of tuberculosis is basically important. A person may step out of the ranks of society for 6 months or a year or even for 18 months without being left too far behind and without losing the will or the ability to take up and go on. This is not so if he is out for 2 or 3 or 4 years. Then his position in business or even in the home will have been filled and he himself will have become too adjusted to the ways of the invalid.

Furthermore the time which each individual may reasonably spend varies tremendously as does the type and strenuousness of the life which he must resume. Some personalities and some age groups can be trusted

to take good care of themselves and others cannot.

Treatment must be chosen and applied with reference to all of these demands and variations and in every instance the patient must be allowed to take a calculated risk never too great but always in proportion to the requirements of his situation. In advanced and desperate cases all of this must be forgotten. In these the patient's very life is at stake and every other consideration is unimportant. But in the great majority of cases the question is not "Will the patient recover?" but "How and when will he recover?" and in these cases the treatment must be cut to fit the situation.

The duration of invalidism is determined by the time required to obtain maximum benefit from rest. In all save exceptional cases bed rest in a sanatorium should be the first phase of treatment. It should be in a sanatorium because only there can the patient be held to the strict regimen and only there can he be adequately educated in the nature of the disease which he must combat. Rest and streptomycin and perhaps

hot is likely to lead to cure because all clearing of exudate and all de-

simply for its own sake because every case should have it. The tuberculosis which one sees on the roentgenogram is never all that is present. Often there is important disease in the hilar lymph nodes and nearly always

are being given a chance to heal.

All bilateral cases unless extension is actual or is too greatly threatened should be continued on rest as long as improvement continues in the hope that one or even both lungs will heal completely so that bilateral collapse can be avoided.

One should not assume that in every case rest and streptomycin will stop progression. All cases must be watched carefully especially those with acute exudative disease. Every patient should have a roentgen ex-

amination each month and the acute cases each week, or two. The course of each case as shown by these roentgenograms must determine whether rest will be continued or whether additional treatment has become necessary.

The improvement obtained from streptomycin and complete bed rest decreases steadily and in something between 6 and 8 months stops completely. It is greatest the first month, less the second, less the third, and so on until finally there is no further change. The time required for this curve to flatten into a straight line determines largely the time required for the arrest of all curable cases. During the first 8 months some lesions will have cleared completely and others in which collapse is to be used as a procedure of choice will already have had it. These cases will be ready for discharge to continue partial rest and graduated exercise at home. Those which have not cleared will have secured maximal benefit from bed rest and must now be considered for collapse or excision or whatever interference seems indicated.

It must be remembered that tuberculosis is a general and not a strictly local disease and that, therefore, every case benefits from a period of bed rest; it must be remembered that the complications of collapse are in proportion to the extent and the acuteness of the disease and that its effectiveness is in proportion to the quiescence of the lesions and the size of the cavities. For these reasons the early use of collapse does not hasten and assure recovery and does not shorten the

ities and the conversion of the sputum, has been established.

But to return to the time element in the treatment of tuberculosis. One should assume that every curable case, even the most advanced, will be arrested and ready to return to work in 18 months. This limit is determined by the time required to obtain maximal benefit from complete bed rest—4 to 8 months—and the time required for the application of and the recuperation from collapse therapy. Many milder cases can return to work much sooner, but even the most

advanced should be well in a year and a half.

Graduated Exercise and Rehabilitation. The formalization of graduated exercise and rehabilitation in the sanatorium, a practice which is being emphasized at the present time, should be avoided. It is in line with the current tendency in social thinking in which the individual is considered as a poor, homeless, jellyfish who has no sense or personal responsibility and who must be continually guarded and guided by the professional psychologist and the trained social worker. Because of this conception, sanatoria are cluttered with people walking by prescription and being so intensively rehabilitated that they never rehabilitate themselves.

The sanatorium should be considered as a place for the enforcement of strict and complete bed rest and for the initiation of collapse measures. If the patient has a home that is at all livable and most persons do, graduated exercise should be taken at home and rehabilitation should be returning to work. He should do all of this under the care and guidance of the physician who has cared for him in the sanatorium. As early as possible he should be put back into his normal milieu and should be treated as a self-responsible, self-reliant individual, and not as a special case who asks or needs prolonged protection and continued aid.

Hemorrhage in Tuberculosis. Hemorrhage in pulmonary tuberculosis is either rapidly fatal or automatically self-limited. If the bleeding vessel is so large that the flow of blood is more than the patient can evacuate by expectoration, he drowns in his own blood in the course of a few minutes. Fortunately, such profuse hemorrhage is rare. In the majority of instances the vessel involved is so small that evacuation of the blood is easy and clotting within the vessel occurs in a few minutes. Hemorrhages of this kind are serious only because of the great chance that aspiration of bacillus-laden blood into uninvolved lung areas will result in wide dissemination of the disease. It is important, therefore, that the bleeding be stopped and that retention of blood in the air passages be prevented.

The bleeding may be stopped by absolute body rest, by the parenteral administration of substances favoring coagulation, or by collapse of the involved lung area. Streptomycin

is of the utmost importance in the prevention and treatment of hemorrhage and also in preventing spread of the disease to new lung areas. The spilling and retention of blood can be prevented by withholding cough reducing narcotics and informing the patient of the extreme importance of ridding himself of the blood by easy throat clearing efforts as fast as it accumulates. Patients tend to suppress cough for fear of stimulating the bleeding and when this tendency is encouraged by the administration of large doses of morphine or codeine retention of blood and dissemination of the disease are almost certain.

The patient should be put on absolute bed rest with an ice bag on the affected side of the chest. Vitamin K and thromboplastin

is copious or continued or if it tends to recur in spite of conservative measures the lung should be collapsed. Collapse by artificial pneumothorax will stop most bleeding almost immediately.

Diabetes and Tuberculosis Diabetes predisposes to infections of all varieties among them tuberculosis. Tuberculosis in the diabetic is more difficult to control than in the nondiabetic and diabetes is more difficult to control in the tuberculous than in the non tuberculous. This greater tendency of tuberculosis to develop and spread in the diabetic is caused by the high blood sugar. The basic problem of the treatment of tuberculosis in the diabetic is therefore the maintenance of a normal blood sugar. Once this has been accomplished and as long as it is maintained the treatment is no different and no more difficult than in the nondiabetic. One must however assume that the blood sugar will not always be kept normal and for this reason must treat the diabetic longer more rigorously and more radically than the nondiabetic. Recovery without collapse should rarely be counted on. Pneumothorax should be used as a procedure of choice even for minimal lesions and once established should be maintained longer than is usual. The permanent collapse of major surgery is resorted to and small

ried out if every effort is made to keep the blood sugar normal and if the treatment is more intense and radical the results will be as good and permanent as in the nondiabetic.

Pregnancy and Tuberculosis The resistance to the development and spread of tuberculosis is greatly reduced during the postpartum period. At this time the disease is peculiarly apt to develop or if already present to be aggravated. For many years young women who had had tuberculosis were advised never to marry or have children and abortion was regularly prescribed for pregnancy in the tuberculous.

With the present methods of treatment these drastic restrictions against childbearing and this indication for abortion save in exceptional circumstances are no longer necessary. Marriage and the bearing of children are important parts of a woman's life and to forbid pregnancy or to terminate it is a serious matter. If the treatment of the disease is carried out with due allowance for this added risk the danger can be largely eliminated. As in diabetes pneumothorax and surgical collapse should be more freely resorted to and pneumothorax should be maintained for a longer period in most instances until 2 or 3 children have been born. Particular precautions should be observed during each postpartum period and as far as possible during the whole period. All in all the situation should be handled in accordance with the modern concept of tuberculosis as an incident in the normal life of the patient rather than as a cause for chronic invalidism.

JEROME R. HEAD

GENITO URINARY TUBERCULOSIS

Genito urinary tuberculosis is usually secondary to tuberculosis elsewhere in the body. Not infrequently the original lesion may be absent or obscure. Unlike tuberculosis of the lungs it is impossible to put the urinary tract at rest. However all other measures such as good food, sunshine and mental and physical rest are helpful in the treatment.

In the past many urologists thought that tuberculosis of the urinary tract attacked only one kidney, the other kidney being free of the disease. A more modern concept now prevails, namely that tubercle bacilli pres-

ent in the urine never occur unless a local lesion is present. Tuberculosis of the kidney may heal and disappear and as a rule the infection is bilateral at its onset. At one time much was made of "autonephrectomy." By autonephrectomy the pathologist described a tuberculosis of the kidney with an obstructed ureter, the patient making what appeared to be a recovery from his infection. This occurs rarely and is not to be hoped for in the ordinary case of tuberculosis.

Medlar found at necropsy that where the urinary tract was infected in tuberculosis the so called healthy or uninfected kidney revealed healed tuberculous lesions.

For many years the treatment of urinary tuberculosis was surgical. In those cases of bilateral renal tuberculosis or where the patient refused surgery the prognosis was indeed grave. Even in unilateral tuberculosis where nephrectomy is done Wildbolz, Emmett and Gile found that the 5 year cures reported from various groups rarely exceeded 50 per cent.

In the past 2 years streptomycin has been used in the treatment of tuberculosis and sufficient time has not elapsed to evaluate accurately its effect. The experience with streptomycin has been sufficient however to show that it stimulates healing in many tuberculous lesions and such complications as poor wound healing, fistulous tracts and tuberculous cystitis. There are some reports in the literature by Nesbit where pus and the tubercle bacilli have disappeared from the urine and the patient appears cured. There is no doubt that we may have to alter our method of treatment as our knowledge of the present and future antibiotics increases.

Tuberculous Bacilluria without Symptoms. Urologists are generally agreed that the kidneys in such cases have organic lesions present. The patient despite the lack of symptoms should be placed in a sana-

torium which serves not only to eradicate the bacilluria but may prevent the development of clinical renal tuberculosis.

Unilateral Renal Tuberculosis. When a patient presents himself with definite clinical symptoms and signs of organic tuberculosis

localized to one kidney judgment must be exercised in individualizing the treatment. If the lesion by pyelogram appears to be a small erosion of a papilla or a fibrotic lesion the use of from 15 to 2 gm of streptomycin daily for 3 months is recommended. A re-examination should be done to evaluate the status of the disease if improvement or cure has been effected. The antibiotic therapy should be continued with careful observation. In the event the disease does not improve or follows a downward course nephrectomy is indicated. Where advanced unilateral renal tuberculosis has progressed to the caseocavernous type with extensive destruction of the kidney it appears that nephrectomy following preliminary treatment with streptomycin is best.

Bilateral Renal Tuberculosis. In these cases the surgeon has been reluctant to advise surgery with much hope. Occasionally the removal of the more seriously affected kidney has resulted in temporary improvement. But usually the added burden on the remaining infected kidney has proved disastrous. Certainly in these patients the use of streptomycin will be of help in prolonging life and comfort for the patient.

Tuberculous Epididymitis. This is seen as a secondary manifestation of tuberculosis elsewhere in the body. Frequently tuberculosis of the urinary tract is discovered with the advent of tuberculous epididymitis. A careful urologic study is indicated in all types of genital tuberculosis. Here likewise preliminary treatment should be with streptomycin, probably followed by epididymectomy when it appears indicated. A more radical operation was recommended by Young, excision of the epididymis, vas deferens, seminal vesicles and prostate. The more radical operation is infrequently attempted.

Tuberculous Prostatitis. This is rarely found as a separate clinical entity. It is not infrequently seen as a complication of urinary tuberculosis. A few cases have been mistaken for carcinoma of the prostate gland and total prostatectomy has been done with poor results. General hygiene, rest, avoidance of sexual activity and conservative measures seem advisable. Streptomycin may be of value but thus far enough experience with this drug has not been reported. Mas-

sage of the gland and local treatment are contraindicated

Tuberculous Cystitis Good results have been reported with the use of streptomycin in cystitis following nephrectomy for tuberculosis. Formerly the cystitis associated with renal tuberculosis continued for months and years following nephrectomy. Various drugs

ent streptomycin gives rapid and dramatic relief in these patients with postoperative cystitis

Tuberculosis of the Penis. This is a rare disease and in most patients appears to be a cutaneous type of disease. The treatment belongs in the hands of the dermatologist

One must realize that the treatment of tuberculosis in general may be radically changed as a result of streptomycin. It would appear that our surgeons are beginning to treat the patient as a person afflicted with a general disease rather than as a person with a localized lesion of the lung, kidney or bone. Undoubtedly surgery will be necessary in many cases where the local lesions are deleterious to health and resist medical treatment

Recent reports in the literature by Youmans and Pyle call attention to the development or appearance of streptomycin resistant bacilli. Their work appears well founded

and the conclusions sound. Whether or not this resistant strain of tubercle bacilli is more virulent or resistant to treatment remains to be determined

In conclusion it should be emphasized that in all cases of tuberculosis of the genitourinary tract co-operation between the attending physician and a competent urologist is important

JAMES I. FARRELL

REFERENCES

- Emmett J. L. and Kibler J. M. Renal Tuberculosis: Prognosis Following Nephrectomy Based on Preoperative Observations in the "Good Kidney." *JAMA* 111:2351 1938
- Cole H. H. Renal Tuberculosis with Special Reference to Follow up Results in Squier Clinic. *Surg Gynec & Obst* 64:1048 1937
- Medlar E. M. Renal Infection in Pulmonary Tuberculosis: Evidence of Healed Tuberculous Lesions. *Am J Path* 2:401 1926
- Nesbit R. M. and Bohne A. U. Present-day Rationale for the Treatment of Urinary Tuberculosis. *JAMA* 138:937 1948
- Pyle, M. M. Relative Numbers of Resident Tubercle Bacilli in Sputa of Patients before and during Treatment with Streptomycin. *Proc Staff Meet Mayo Clin* 22:465 1947
- Wildbolz H. Renal Tuberculosis. *J Urol* 21:145 1929
- Youmans G. P. and Williston E. H. Streptomycin resistant Variants Obtained from Recently Isolated Cultures of Tubercle Bacilli. *Proc Soc Exper Biol & Med*, 68:458 1943

FUNGOUS DISEASES

ACTINOMYCOSIS

[Lumpy Jaw Streptothricosis Nocardosis]

Actinomycosis may be divided into the localized and well circumscribed type and the systemic type. The localized type usually has a favorable prognosis. The systemic type in the past usually resulted in death. The treatment usually relied on has been iodine and its salts, potassium and sodium iodide, copper sulfate, thymol, vaccines, roentgen rays, radium and surgery. With the onset of the era of the newer chemotherapeutic agents the prognosis of systemic actinomycosis has become much more favorable except in well advanced cases with extensive involvement of the brain tissue

In spite of the newer chemotherapeutic

agents the old mainstays still have a place in the treatment of actinomycosis but usually in combination with sulfonamides and penicillin. Each case is a problem in itself and the type or combinations of treatment must be judged accordingly

The choice of treatment should depend upon the location, type, duration, extent and severity of the lesion. For the primary cutaneous type one form of therapy, usually the sulfonamides or penicillin, is sufficient. For the extensive cases and the systemic type a combination of several forms of treatment gives the best results

Sulfonamides. In the primary cutaneous type one of the sulfonamides, preferably sulfadiazine or penicillin, is recommended. If sulfadiazine is the drug of choice it is ad-

ministered as follows 2 gm at the beginning followed by 1 gm every 4 hours so that a satisfactory level in the blood is obtained This is continued until the lesion shows evidence of clearing and is then reduced so that a blood level of 5 to 10 mg per 100 cc is maintained A close watch for complications such as blood dyscrasia hematuria and skin eruption should be kept Exposure to the sun should be avoided while the sulfonamides are administered because of photosensitization

Penicillin If the organism is found to be sensitive to penicillin this antibiotic is preferable to the sulfonamides because of the less serious complications likely to accompany the administration of the drug Penicillin 50 000 units given intramuscularly every 3 hours around the clock is recommended Penicillin 300 000 units in yellow wax and peanut oil every 12 hours may be used in ambulatory cases If the patient proves to be sensitive to the vehicle crystal line penicillin which is water soluble may be employed in doses of 200 000 units three times a day

In systemic or extensive actinomycosis the ideal treatment is

- (1) A high calorie and high vitamin intake to build up the natural resistance of the patient
- (2) Ferrous sulfate 0.2 gm t.i.d. if hypochromic anemia is present
- (3) Bed rest

Penicillin 50 000 units intramuscularly every 3 hours may be given partly by the continuous intravenous drip method and partly by intramuscular injection as recommended by Hendrickson and Lehman In cases of central nervous system involvement well diluted penicillin can be given intrathecally (50 000 units daily)

A sulfonamide preferably sulfadiazine should be given starting with 2 gm and then 1 gm every 4 hours being continued until the patient appears to be clinically well and then for prophylactic reasons the sulfonamide should be continued in doses of 1 gm four times daily gradually reduced to 3 gm and 2 gm daily for a period of several months if any signs of relapse are noticed intensive therapy should again be resumed

Surgery should be postponed until after several doses of sulfonamides and penicillin

have been administered except in cases in which immediate surgical intervention is necessary to relieve pressure and to alleviate pain Adequate surgical drainage is important All sinus tracts should be exposed and drained Necrotic tissue should be removed wherever possible In cases of intestinal actinomycosis resection of loops of intestine may be necessary Lobectomy and pneumonectomy are justified only when all other forms of treatment have been tried and failed

Röntgen therapy may be of value as a supplementary treatment especially in cases of indolent lesions Good results have been reported with fractional and intensive therapy with and without filtration

Iodides These may be given as a saturated solution of potassium iodide starting with 15 drops three times a day orally and increasing 3 drops daily to the point of tolerance Sodium iodide may be administered intravenously in 1 gm doses once a day in place of potassium iodide Tincture of iodine

in milk 3 times a day to the point of therapy Ethyl iodide inhalation therapy is of particular value in cases with bronchopulmonary involvement because it is the most direct route Ethyl iodide is nontoxic and highly volatile The coefficient of distribution between the alveolar air and the

demonstrated moreover that only a small proportion is returned in the venous blood so that the tissues are exposed to relatively large amounts of iodine The initial dose is 15 cc (3 gm) this is increased by 0.5 cc (1 gm) per dose until 3 cc (6 gm) is reached or in large patients 4 cc (8 gm) It usually requires about 30 minutes to inhale a dose of 3 cc of the mixture The necessary amount may be given in fractional doses during the day if the patient is too sick to inhale it all at one time To avoid cumulative effects inhalations are given on 2 successive days and then omitted on the third day It is advisable to use a mineral oil spray once a day to avoid irritation or an uncomfortable dry sensation in the throat A discussion of contraindications and pos-

sible complications is presented in the fol-

sules (of 1 or 2 gm) once a day has been used as a supplementary treatment although the writer considers iodide in any form mentioned above preferable

Copper sulfate ($\frac{1}{4}$ gr) given by mouth or colloidal copper administered intravenously has been used. This form of therapy is not recommended.

Local treatment by irrigation with penicillin Lugol's solution or with 1 per cent gentian violet is of value.

Vaccine Therapy This has been used with some success as a supplement to surgery. It may supplement sulfonamide or penicillin therapy or both if the patient fails to respond. Colebrook recommends both stock and autogenous vaccine in doses of 5 000 000 to 10 000 000 mycelian fragments at intervals of 5 days.

Streptomycin Streptomycin has not been used in a sufficient number of cases of actinomycosis for one to evaluate its therapeutic index in this particular disease. Scattered reports have appeared in the literature. Costigan reports the cure of a severe case of actinomycosis within 5 days after the institution of treatment with streptomycin 250 000 units in 2.5 cc of sterile water every 3 hours. The same patient did not respond to iodides, penicillin and sulfonamides.

JACOB H. SWARTZ

REFERENCES

- Benbow E P Jr, Smith D T and Grimson A S: Sulfonamide Therapy in Actinomycosis. 2 Cases Caused by Aerobic Partially Acid Fast Actinomyces. *Am Rev Tuberc* 49:395 1944
- Costigan P C: Case of Actinomycosis Treated with Streptomycin. *Canad M A J* 56:431 1947
- Hamilton A J C and Kirkpatrick H J R: Actinomycosis Successfully Treated with Penicillin. Report of 2 Cases. *Brit M J* 2:728 1945
- Hendrickson G G and Lehman E P: Cervicofacial Actinomycosis Successfully Treated by Penicillin without Surgical Drainage. *JAMA* 128:495 1945

Muskatblat E: Primary Actinomycosis of Skin. Report of Case. *Arch Dermat & Syph* 56:708 1947

Pillsbury N R and Wassersug J D: Pulmonary Actinomycosis. Treatment with Sulfonamides. *New England J Med* 230:72 1944

Randall O S: Early Diagnosis and Surgical Treatment of Actinomycosis of Head and Neck. *Am J Surg* 57:433 1942

Rashbaum M and McIntosh H C: Pelvic Actinomycosis Treated by Surgery and Roentgen Ray with Recovery. *Am J Obst & Gynec* 47:849 1944

BLASTOMYCOSIS

In the treatment of North American blastomycosis supportive measures such as a high vitamin and high calorie diet, rest and sunshine are essential, particularly in the systemic type. Complete studies including roentgen ray and spinal fluid examinations should be done to determine whether dissemination to internal organs has taken place, since the prognosis is much poorer particularly when there is central nervous system involvement.

Iodides Although iodide therapy is still the most effective weapon in this disease one must continue to search for more specific and effective therapeutic agents especially for systemic blastomycosis. Iodide therapy was first used in cutaneous blastomycosis by Gilchrist. Best results are obtained if the iodides are supplemented by roentgen therapy and surgical procedures whenever indicated. The administration of iodide should be continued until all signs of active disease have disappeared.

Martin and Smith advise desensitization with blastomycin in hypersensitive patients before iodide therapy is instituted. They report an adverse effect resulting in the spread of the infectious process in hypersensitive cases when iodides are administered without at least partial desensitization for about 2 weeks. They recommend the following technique: A skin test with a standardized heat-killed blastomycin vaccine is done by injection intracutaneously of 0.1 cc of the vaccine. The size of the maximal reaction is determined by observation of the site of injection at intervals of 24 and 48 hours. A reaction of 1 cm or more in diameter indicates hypersensitivity. The size of reaction observed determines the dilution

of the vaccine required for the first desensitization. A dilution of 1:100 is used for the first injection if the reaction is from 1 to 2 cm. in diameter. A 1:1000 and 1:10,000 dilution is used for reactions of 2 cm. and 3 cm. in diameter respectively. The proper dilution is injected subcutaneously beginning with 0.1 cc. This dose is increased by 0.1 cc. until 1 cc. is reached. Injections are given three times a week. This procedure is repeated with each lower dilution until undiluted vaccine is used. A local or general reaction is a sign to stop injections. These may be resumed several days later with a dilution $\frac{1}{10}$ th as strong as the one that produced the reaction. Complete desensitization is not to be expected but a definite reduction in the size of the erythematous reaction takes place indicating a decrease in hypersensitivity.

The most common type of iodide used is a saturated solution of potassium iodide in water or milk starting in the hypersensitive cases with as low a dose as 3 drops three

times a day as evidenced by a skin rash or running nose the drug should be stopped until all signs of iodism have disappeared and then resumed beginning with 3 drops three times a day and increasing by 1 drop daily until a dose of 20 drops three times a day is reached. This dose should be continued until all active signs of the disease have disappeared. In cases that do not show hypersensitivity to the intracutaneous injection of blastomycin a dose beginning with 15 drops three times a day and increased by 1 drop per dose to the point of tolerance is advisable.

intravenously are advisable.

Ethyl iodide inhalations are particularly useful in systemic blastomycosis with pulmonary involvement. Potassium iodide may be given orally as supplemental therapy. The dosage of ethyl iodide and the indications and contraindications are discussed in the section on moniliasis. Ethyl iodide inhalations have been employed successfully by the writer and by others in the treatment of blastomycosis. However failure to obtain permanently good therapeutic results in

enough of the severe cases makes it necessary to search for a more specific therapeutic procedure.

Copper sulfate in doses of $\frac{1}{4}$ to 1 grain (15 to 60 mg.) administered orally three times daily has been reported effective. The writer has had no experience with this form of therapy.

Surgery Surgical removal of small and accessible foci is good treatment. Large foci of infection may be drained. Conant et al. recommend deferring surgery until at least partial desensitization with blastomycin has been accomplished. Surgical diathermy or actual cautery is not contraindicated.

Roentgen Rays In cutaneous blastomycosis the use of filtered roentgen rays is advisable when surgical excision is not possible. The dosage advised is 75 to 100 r. filtered through 1 mm. aluminum once a week. It is not advisable to exceed a total dose of 1200 to 1500 r. Conant et al. warn against the use of roentgen therapy in patients with hypersensitivity to blastomycin before partial desensitization with injections of blastomycin vaccine has been produced.

Vaccinotherapy Scattered reports of clinical improvement with vaccine injections have been presented. Except for desensitization in cases with hypersensitivity as a supplemental treatment the value of specific vaccinotherapy is questionable.

Antiblastomycosis Rabbit Serum Martin reports the use of antiblastomycosis rabbit serum with occasional benefit.

Sulfonamides Several questionably favorable reports on the therapeutic effectiveness of the sulfonamides have appeared in the literature. Most of the reported results coincide with our experience in revealing the sulfonamides to be ineffective. Kenney demonstrated that sulfonamides are of no value in blastomycosis. Noon and Callaway found the concentrations required in vitro for inhibition of growth of *Blastomyces dermatitidis* to be well above the maximal clinical drug levels tolerated. They therefore concluded that the sulfonamide compounds would be ineffective if used orally or parenterally in the treatment of blastomycosis.

Streptomycin and Penicillin *Blastomyces dermatitidis* is rather resistant to both of these antibiotics. Their therapeutic value in this disease is doubtful.

Streptothricin Because of its high toxicity, it is doubtful whether this drug will have clinical therapeutic value in blastomycosis, with the possible exception of its use as a

allantoic membrane of the developing chick embryo

Glitoxin According to Meyer and Ordal glitoxin showed a high fungistatic action in vitro on *Blastomyces dermatitidis* but was extremely toxic to the chick embryo

In South American blastomycosis iodide therapy has been reported effective in some cases by De Almeida The mode of administration is the same as that for North American blastomycosis Sulfonamides have been reported effective if given over a long period

JACOB H SWARTZ

REFERENCES

- Keeney E L Medical Mycology *M Clin North America* 29 323 1945
- Martin D S Practical Application of Some Immunologic Principles to Diagnosis and Treatment of Certain Fungal Infections *J Invest Dermat* 4 471 1941
- Martin D S and Smith D T Blastomycosis (American Blastomycosis Gilchrist's Disease) Review of Literature *Am Rev Tuberc*, 39 275 1939
- Martin D S and Smith D T Blastomycosis (American Blastomycosis Gilchrist's Disease) Report of 13 New Cases *Am Rev Tuberc* 39 488 1939
- Meyer E and Ordal Z J Action of Streptothricin and Other Antibiotic Agents on *Blastomyces dermatitidis* Infections of the Chick Embryo *J Infect Dis* 79 199 1946
- Noon J O and Callaway J L Action of Sulfonamide Compounds on *Blastomyces dermatitidis* in Vitro *Arch Dermat & Syph* 47 620 1943

COCCIDIOIDOMYCOSIS

No specific drug is known for the treatment of this disease It is my belief and hope that a new antibiotic will be discovered that will prove specific

In a discussion of treatment it is more practical to discuss first the treatment of the primary pulmonary type and then the management of progressive coccidioidomycosis

Primary Pulmonary Coccidioidomycosis. The object of treatment is to afford the patient optimal conditions for localizing the infection Rest in bed is indicated until the temperature, white cell count, and sedimentation rate are normal, and the pulmonary

reliable index of the activity of the infection Symptomatic treatment, such as salicylates with or without codeine, may be administered Supportive treatment consisting of a high vitamin and high calorie intake during the convalescent stage is valuable Before the patient is discharged the physical signs

no specific treatment for progressive coccidioidomycosis The variety of drugs used in the past including the more recently tried sulfonamides and penicillin has not proved effective However, since there are some scattered reports of cures, present methods of treatment should be considered

Regardless of which type of therapy is tried, every effort should be made to support the general resistance of the patient by rest in bed and a high calorie and high vitamin intake

Since hypersensitivity to coccidioidin is a striking feature in the early stages of progressive coccidioidomycosis it seems logical to proceed with desensitization of the patient with coccidioidin, followed by the administration of iodine therapy Martin and Smith have developed a program for desensitization in cases of blastomycosis (This method has been described previously in the section on the treatment of Blastomycosis) Among various types of iodine therapy, potassium iodide has been most extensively used The writer considers ethyl iodide in halation therapy more logical, since it is a more direct route and a greater concentration can be obtained The initial dose is 15 cc (3 gm), this is increased by 0.5 cc (1 gm) per dose until 3 cc (6 gm) is reached A dosage of 4 cc (8 gm) has been used in some cases The amount may be given in fractional doses during the day or at one sitting To avoid cumulative effect, inhalations

are given on 2 successive days and then omitted on the third day. A discussion on contraindications and possible complications is presented in the following section on treatment of Moniliasis.

Röntgen Therapy This is useful only in aiding the absorption of the exudate in the granulation process and in the relief of pain. It is therefore valuable as a supplementary treatment. Intensive or semi-intensive dosage may be used.

Vaccinotherapy Supplemented by injection of colloidal copper vaccine has been reported effective by Jacobson. He recommends a special extract of the organism prepared by mixture of equal parts of the filtrate from a broth culture and the filtrate from the macerated organisms. The coccidioidin is injected cutaneously every 8 to 14 days depending on the degree of local and constitutional reactions. The colloidal copper is given as intragluteal injections in dosages of 5 cc every 4 to 7 days depending on systemic reactions. Jacobson does not mention the number of injections required. This probably depends on the course of the disease.

Miscellaneous *Gentian violet* is highly toxic and should be used cautiously administered intravenously in 0.25 per cent solution. The total dose should not exceed 5 mg of the dye per kilogram of body weight.

Antimony and potassium tartrate were used by Guy and Jacob and by Tomlinson and Bancroft in combination with roentgen rays and the results were reported good. The authors recommend from 2 to 8 cc of a 1

mental course of the disease. The treatment of patients with pulmonary cavities is still in an unsettled stage. Such patients are apparently immune to dissemination. Evidence of the local spread of the fungus from the cavities to adjacent pulmonary tissue has not been demonstrated. Most cavities ultimately heal spontaneously. There is a difference of opinion whether or not active treatment such as pneumothorax, thoracoplasty, or lobectomy should be used even when the cavities persist for a long time.

JACOB H. SWARTZ

REFERENCES

- Demenholz E J and Cheney G. Diagnosis and Treatment of Chronic Coccidioidomycosis. *Arch Int Med* 74:311 1944.
- Dickson E C. Primary Coccidioidomycosis: Initial Acute Infection with Results in Coccidioidal Granuloma. *Am Rev Tuberc* 38:722 1938.
- Goldstein D M and McDonald J B. Primary Pulmonary Coccidioidomycosis: Follow up of 75 Cases with 10 More Cases from a New Endemic Area. *JAMA* 124:557 1944.
- Rosenberg H F, Dockerty M B and Meyerding H W. Coccidioidal Arthritis: Report of Case in Which Ankles Were Involved and Condition Was Unaffected by Sulfanilamide and Roentgen Therapy. *Arch Int Med* 69:238 1943 correction 69:717 1943.
- Smith C E. Coccidioidomycosis. *M Clin North America* 27:790 1943.
- Swartz J C F and Gillespie J B. Clinical and Roentgenologic Aspects of Coccidioidomycosis. *Am J M Sc* 212:652 1946.

HISTOPLASMOSIS

(Reticulo endothelial Cytomycosis)

No specific therapy for histoplasmosis has had a fair trial since most of the cases have been diagnosed post mortem and the few cases treated have been diagnosed late in the course of the disease. It is therefore essential that a diagnosis of histoplasmosis should be considered in the differential diagnosis in patients with anemia, leukopenia, cachexia, intermittent pyrexia, lymphadenopathy and splenomegaly.

Iodides Iodides in any form have not proved effective therapeutically.

Arsenicals Fowler's solution, potassium arsenite, arsphenamine, neoarsphenamine and mapharsen have had no effect on the course of histoplasmosis.

Other Drugs Bismuth, quinine and pent-

is capsule form and given in daily doses of 1 to 6 gm locally. This remedy may be applied as a 33.3 per cent solution in olive oil.

Immunotransfusion has been used but its value is doubtful. Goldstein and McDonald treated 2 patients with high titer convalescent blood with resulting improvement.

Surgery Surgery in the form of incision and drainage of abscesses with concurrent use of penicillin to minimize secondary infection can be undertaken with impunity. Surgical removal of fungating cutaneous lesions may be done with good results. It is obvious, however, that removal of such lesions exerts no influence on the funda-

nucleotide, with or without supplementing liver, iron, or vitamins, have not proved effective in changing the course of the disease to a favorable outcome

Antimony. Meleney recommends the antimony preparations such as antimony sodium tartrate, the trivalent organic compounds such as fuadin, or the pentavalent preparation such as subamine glucoside (neostam) Mantel, Troy, and Kendall report clinical improvement in one case treated with neostam

Sulfonamides Curtis and Grekin report a proved case of histoplasmosis treated with sulfadiazine orally, 8 gm daily up to a total dose of 576 gm All lesions cleared, but organisms were still demonstrable in sections at discharge The authors report a second proved case in which the patient recovered completely except for chronic lymphostasis The last biopsy specimen did not reveal the organism This patient received a total of 522 gm of sulfadiazine in 87 days The second case is a good example of possible favorable therapeutic results with sulfonamides in cases diagnosed early before dissemination takes place Baliña et al reported the arrest of the disease in one case of mucocutaneous involvement with the administration of sulfonamides orally and the local application of this drug Although these reports sound encouraging according to the literature there are still more failures with sulfonamides than good therapeutic results

Penicillin The therapeutic results reported with the use of penicillin have not been favorable Seabury and Drygas observed no response to penicillin therapy in 2 cases Davis and Neff describe 2 failures with the use of penicillin Similar reports have appeared

Surgery I believe that in a case in which the lesion is accessible and isolated before dissemination has taken place surgery should be of value I have had no opportunity of determining whether desensitization with histoplasmin vaccine is necessary before surgery is undertaken However, because of the close relation between the micro organisms of *Blastomyces dermatitidis* and *Histoplasma capsulatum* as evidenced by the cross immune reactions, one would deduce that desensitization in hypersensitive cases

would be advisable just as it is in blastocosis

Röntgen Rays The reports indicate the roentgen ray is not an effective therapeutic agent in histoplasmosis

cc, sulfonamides or neostam Every case should be made to diagnose the disease early and thus to start treatment before dissemination has taken place

JACOB H SWARTZ

REFERENCES

- Anderson, W A D, Michelson, I D, and L T M Histoplasmosis in Infancy, Report of 1 Case. *Am J Clin Path*, 11 344, 1941
 Baliña, F L et al Third Case of Histoplasmosis Recorded in Argentina Sulfonamide Therapy. *Rev argent dermatosif*, 27 453, 1943 abs
Trop Dis Bull, 41 421, 1944
 Curtis, A C, and Grekin, J N Histoplasmosis: Review of Cutaneous and Adjacent Mucous Membrane Manifestations with Report of 3 Cases. *JAMA*, 134 1217, 1947
 Emmons, C W, Olson, J H, and Eldridge, W Studies of Role of Fungi in Pulmonary Disease. Cross Reactions of Histoplasmin. *Publ Hlth Rep*, 60 1383 1945
 Meleney, H E Histoplasmosis (Reticulo-

- Treatment of Histoplasmosis. *Am J Clin Path*, 11 344, 1941
Int Med, 25 340, 1946
 Ziegler, E E Histoplasmosis of Darling. Review and Case Report with Autopsy. *Ann Int Med*, 24 1073, 1946

MONILIASIS

The treatment of moniliasis at best is too successful Newer and more effective treatment is necessary It is my belief that successful therapy will depend on the discovery of new agents, which through either stimulation of immune reaction or direct fungistatic or fungicidal action will bring about a cure of a disease that at present is most resistant, particularly in its general cutaneous and systemic types

For the sake of simplicity treatment will

ough investigation of the diet, hygiene, parathyroid disease, and diabetes is essential

Localized Types CHRONIC PARONYCHIA
It is essential to instruct patients of the danger to their hands in frequent immersion in water, especially dishwater, and that they should avoid handling unwashed vegetables and fruits. It is advisable to protect the hands with cotton and rubber gloves if dishwashing and the handling of fruits and vegetables are necessary.

Local treatment consists of warm soaks in a saturated solution of boric acid for 10 to 15 minutes, morning and night, followed by the application of the following ointment: 2 per cent mercurochrome crystals, 4 per cent water, and 11 per cent salicylic acid with the addition of vaseline and lanolin. Greenwood and Rockwood recommend the application of sodium perborate paste morning and night.

Röntgen therapy has proved effective in doses of 50 to 75 r, unfiltered. In my opinion this treatment is effective not because of its fungistatic and fungicidal action but because of its effect on chronic inflammatory tissue.

EROSIO INTERDIGITALIS BLASTOMYCETICA
This condition may occur alone or may accompany chronic paronychia. The protec-

used. The local treatment found most effective is the use of warm boric acid solution compresses followed by the application of a 5 per cent solution of mercurochrome. Bacterial fuchsin solution (1 per cent) may be used instead of mercurochrome. Treatment is carried out twice daily.

VESICULOPUSTULAR AND ECZEMATOUS MONILIASIS
The local treatment is as follows: Any one of the following ointments may be found effective, being applied once or twice daily.

Ointment	Per cent
(1) Bacterial fuchsin	10
Zinc oxide	60
Starch	60
Vaseline (qs ad)	

(2) Mercurochrome crystals	20
Water	40
Salicylic acid	30
Vaseline	
Lanolin (aa, qs, ad)	
(3)* Caprylic acid	100
Diethylene glycol mono-ethyl ether	30
Carbowax (6000)	47.5
n-propyl alcohol	10.0
Zinc caprylate	5.0
Sodium hydroxide	2.45
Water	22.05

* Obtainable from Mycoloid Laboratories, Little Falls, N. J.

The amount of sodium hydroxide may vary since enough is added for adjustment to a reaction of pH 8.0.

The last ointment has been used successfully and reported by Keeney.

INTERTRIGENOUS MONILIASIS
Obesity, diabetes and mechanical and physical factors causing heat, moisture, and maceration in the folds as well as poor hygiene, should be considered and corrected whenever possible. The local treatment is the same as that advised above for *erosio interdigitalis blastomycetica*.

PERLECHE
In all cases of perleche the possibility of a dietary deficiency, particularly riboflavin deficiency, should be considered. Poorly fitting dentures, producing mechanical irritation and a good soil for prolific growth of *Candida albicans*, which normally occurs in the mouth, should be corrected.

Locally, the application of an ointment made up of 2 per cent salicylic acid, 2 per cent sulfur precipitate, and petrolatum is helpful.

I have found cauterization with a hot needle or a fine high frequency spark effective as a supplementary treatment.

INTRA ORAL THRUSH
When this condition is seen in infants, the source of infection may be a monilial vaginitis in the mother, or a chronic paronychia, or *erosio interdigitalis blastomycetica* in the mother or the nursemaid. Malnutrition is another underlying cause. These factors should therefore be considered in the treatment of thrush in infants. In older children and adults the condition is more resistant. It may be part of the symptom complex of systemic or generalized

cutaneous moniliasis. It may be associated with a systemic disease such as diabetes, malnutrition or parathyroid dysfunction. Investigation and correction, if possible, are therefore essential for good treatment.

The local treatment is not too satisfactory, especially when intra oral thrush is part of a generalized cutaneous or systemic moniliasis. In these cases local therapy at best gives only temporary relief. The following local treatment has been tried and is recommended.

- (1) Sodium perborate (3 dr to $\frac{1}{2}$ glass of water) as a mouth wash three times a day.
- (2) Gentian violet (1 per cent aqueous solution) painted on the involved areas once a day. Treatment should be stopped if there are any signs of irritation.

The sodium salts of propionic, valeric, caprylic, capric and undecylenic acids are fungistatic and fungicidal in varying degrees for the different pathogenic fungi when tested in vitro. Of these fatty acid salts sodium caprylate is particularly effective against *Candida (monilia) albicans*. Keeney therefore recommends a 20 per cent aqueous solution of sodium caprylate adjusted to a reaction of pH 7.4 applied to the lesions in the mouth every 2 hours with swabbing of the entire mouth twice daily. My experience with 2 cases of intra oral thrush associated with cutaneous and onychial involvement did not parallel those reported by Keeney. However, more cases need to be treated before a correct evaluation of the effectiveness of such treatment can be made.

Autogenous vaccine therapy has not been successful in my experience.

VULVOVAGINITIS. Systemic causes such as diabetes and deficiency diseases as well as local gynecologic causes should be looked for and corrected wherever possible. Vulvovaginitis may be associated with generalized cutaneous or systemic moniliasis, the treatment for which is discussed below.

The local treatment as recommended by Alter et al. consists in the application of a jelly like mixture of 20 per cent equal parts of calcium and sodium propionate in a tragacanth base and buffered at a reaction of pH 6.5. The following is a good formula.

Drug	Per cent
Calcium propionate	95
Sodium propionate	95
Propionic acid	10
Glycerin	100
Bentonite	320
Water	350

Gentian violet douches diluted 1:10,000 given three times a week or less frequently, if there is any sign of irritation, are of value. Lewis recommends a vaginal suppository (0.13 gm. to each). Hesseline employs Lugol's solution diluted to one-quarter

each night two capsules containing a mixture of potassium iodide and potassium iodate (62 parts of potassium iodide to 1 part of potassium iodate). Capsules of 00 to 000 are employed. The drugs are diluted and mixed with kaolin so that each capsule contains about 0.125 gm. of the iodides.

In our experience the best results in cases of localized vulvovaginitis have been obtained with 1 per cent bacterial fuchsin solution painted on twice a day and a daily cleansing douche of sodium bicarbonate ($\frac{1}{2}$ teaspoonful to a pint of water). The vulvovaginitis associated with generalized cutaneous or systemic moniliasis does not respond readily to local treatment.

Autogenous vaccino-therapy has not proved to be successful.

Generalized Cutaneous and Systemic Types. There is no known effective cure for these types of moniliasis. The only hope lies in the discovery of new and effective antibiotics. Search for new antibiotics is being carried on in many laboratories.

Therapy should be directed toward the eradication of all foci of infection. Unfortunately with the present armamentarium that is almost an impossible task to carry out, especially if the focus is in the gastrointestinal tract. Complete study of the patient is essential with particular emphasis on diabetes, nutritional factors, hygiene and parathyroid disease. These studies should include roentgen examination of the chest to determine the presence or absence of bronchopulmonary involvement.

A high vitamin, high calorie diet, ren-

forced by components of the vitamin B complex and liver therapy ■ helpful

Iodide therapy particularly ethyl iodide inhalation has proved most effective in bronchopulmonary moniliasis probably because the coefficient of distribution between the alveol

sufficiently

relatively

blood stream ■ it has also been demonstrated that ■ small proportion is returned in the venous blood so that the tissues are exposed to relatively large amounts of iodine. In bronchopulmonary moniliasis inhalation therapy is a more direct route. The initial dose of ethyl iodide is 1.5 cc (3 gm) This

given on two successive days and skipped on the third day to avoid cumulative effect. A mineral oil spray to avoid irritation of the throat may be used once a day. The inhaler of choice* is designed to allow a comfortable mixture of ethyl iodide† and air to be inhaled. It is important that the ethyl iodide be free from impurities particularly phosphorus. This can be accomplished by proper distillation.

The most common complication is the usual papulopustular eruption occurring particularly on the face and upper part of the trunk. The eruption usually disappears a few days after the drug has been discontinued. Treatment may then be resumed without ill effect in most cases. A more severe pemphigoid eruption should be a signal to discontinue the drug and not to resume its use after the eruption has cleared since the second attempt may result fatally. Peripheral neuritis should be watched for although it is a rare complication. This complication is probably due to the ethyl radical. If such a complication occurs treatment should be discontinued.

Other forms of iodine therapy may be used. Saturated solution of potassium iodide starting with 15 drops three times a day orally and increased ■ drops daily to the

point of tolerance ■ most commonly administered Sodium iodide intravenously may be given in 1 gm doses once a day. Tincture of iodine in milk or water starting with 5 drops three times ■ day and increasing the dose to the point of tolerance is another form of iodine therapy.

Martin and Smith recommend desensitization with monilia vaccine in hypersensitive patients before any course of iodine therapy is started. (The technic is outlined previously in the section on Blastomycosis.)

Keeney has given sodium caprylate intravenously but the sclerosing action on the veins has made its protracted use impossible. Vaccinotherapy both autogenous and

and monilia extracts alone and in combination

Hiatt and Martin describe a dramatic recovery in a case of bronchopulmonary moniliasis treated with anti *Candida* (monilia) *albicans* rabbit serum. The patient was given injections subcutaneously beginning with 0.1 cc of a 1:10 dilution and the dose was increased by 0.1 cc daily until 0.9 cc was reached. The desensitization series was repeated twice. This good result was obtained in a patient with a negative skin test to *Candida* vaccine, a negative complement fixation test and a positive immediate reaction to an anti *Candida albicans* rabbit serum. The writer has tried this form of therapy in 2 cases with generalized cutaneous and mucous membrane involvement without beneficial therapeutic results. In one case no tests for sensitivity were done. In the other the test to viomycin showed at the end of 48 hours an erythematous reaction slightly larger than 1 cm in diameter. The reaction to anti *Candida* rabbit serum was erythematous and nonelevated; no pseudopod was observed.

This writer is using serum from patients who have recovered from chronic paronychia caused by *Candida* (monilia) *albicans* as ■ therapeutic agent. The results and proper technic will appear in ■ later publication after more work has been done.

JACOB H. SWARTZ

* The inhaler may be obtained from Warren Colins Boston Mass.

† Purified ethyl iodide may be obtained from Burham Soluble Iodine Company, Aulandale, Mass.

- Keeney, E. L. Medical Mycology *M Clin North America*, 29 323, 1945
- Kramer, L., et al Case of Systemic Torula Infection with Tumor Formation in Meninges *J Neurol Neurosurg & Psychiat*, 9 158, 1946
- Mezey C. M., and Fowler, R. Cerebrospinal Cryptococcosis *JAMA*, 132 632, 1946
- Voyles G. Q., and Beck, E. M. Systemic Infection due to *Torula histolytica*, Report of 4 Cases and Review of Literature *Arch Int Med*, 77 501, 1926

SPOROTRICHOSIS

Potassium Iodide This is the most effective weapon in the treatment of this disease. It is administered orally, beginning with 10 drops of a saturated solution three times a day and increasing by 3 to 5 drops per dose daily until tolerance is reached—usually 30 to 40 drops three times a day. This maximal dose is maintained. Potassium iodide is best given in water or milk. This treatment should be continued for at least 1 or 2 months after apparent complete recovery. If this drug is not tolerated orally, sodium iodide in daily doses of 1 gm may be given intravenously.

Another method of iodide therapy is by iontophoresis. Shaffer and his associates reported good results with daily treatment for a total of 13 weeks. They used a strong solution of iodine U.S.P. diluted 1:100 in isotonic solution of sodium chloride and increased to 1:50 after 7 weeks. Since the active ion, iodine, is an anion, the negative electrode was attached to the involved parts and the indifferent positive electrode was placed on the back. The current was about 15 ma for 20 minutes in the first week and was gradually increased to about 35 ma for 30 minutes.

In the rapidly spreading or fulminating type and in systemic sporotrichosis it is wise to administer potassium iodide orally and ethyl iodide by inhalation. (The technique and dose are described in the section on Actinomycosis.)

Iodide probably does not act as a direct fungicide. Cure may result because of the stimulation and proliferation of fibroblastic tissue and encapsulation of the organism.

Surgery Surgery and cauterization are contraindicated because such procedures are frequently followed by prolonged suppuration and ulceration and retard rather than effect a cure. However, in cases of fluctuation, incision and drainage may have to be

attempted. Aspiration of the pus may be adequate and should be tried first.

Miscellaneous Roentgen therapy to local lesions is a useful supplement in semi-intensive dosage with filtration.

Autogenous and stock vaccine has not proved its value, but in resistant cases may be used in conjunction with iodide therapy.

Sulfonamides have been employed with good results in some cases.

Penicillin and streptomycin have not produced good therapeutic results in this disease. The results obtained with iodide therapy far surpass those in patients treated with the known antibiotic agents.

JACOB H SWARTZ

REFERENCES

- Leiby, G. M., Sulzberger, M. B. and Baer, R. L. Sporotrichosis in New York State. Report of 2 New Cases and Tabulated Discussion of 26 Previous Ones. *Arch Int Med*, 75 145, 1915
- Moore, M. Practical Points in Diagnosis and Treatment of Actinomycosis and Sporotrichosis. *Post grad Med*, 1 281, 1947
- Shaffer, L. W., and Zackheim, H. S. Sporotrichosis. Report of Case in Which Treatment with Iontophoresis Was Successful. *Arch Dermat & Syph*, 56 244, 1947

MADUROMYCOSIS

Since maduromycosis (Madura foot, mycetoma) may be caused by a variety of fungi belonging to different species, no one specific drug is effective. Iodides, thymol, copper sulfate, and antimony compounds are not helpful. Sulfonamides and penicillin are useful indirectly in taking care of the usually present superimposed bacterial infection which is frequently the cause of death and directly in cases caused by actinomycetes. (The dosage and course of treatment are discussed in the section on Actinomycosis.) Conservative surgery, such as excision of localized early lesions, or radical surgery, such as amputation in the more extensive cases, may be necessary.

JACOB H SWARTZ

REFERENCES

- Carlos, C. M. Madura Foot (Mycetoma). First Report from Isthmus of Panama. *Arch Dermat & Syph*, 55 761, 1947
- Dixon, J. M. Sulfanilamide Therapy in Madura Foot. *Virginia M Monthly* 68 281, 1941

Fienberg R. Madura Foot in Native American Case of Monosporosis *Am J Clin Path*, 14:239 1944

Twining H E, Dixon H M and Weidman F D Penicillin in Treatment of Madura Foot Report of 2 Cases *U S Nav M Bull*, 46:417, 1946

GEOTRICHOSIS

Cases of bronchopulmonary geotrichosis have been reported. Oral and intestinal forms of the disease have also been described. Since species of *Geotrichum* are frequently found in the mouth and intestinal tract of normal persons, caution must be used before this organism is blamed for producing disease. The writer and his co-workers have grown pure cultures of *Geotrichum* from the stools of patients with ulcerative colitis compared with few scant colonies from the stools of normal persons and from those with diarrhea from other causes.

Ethyl iodide inhalation therapy is advisable in the pulmonary type. Rest and a high vitamin intake are as essential as in any other systemic disease. Pulmonary tuberculosis must be ruled out before any iodide therapy is instituted.

Oral *geotrichosis* may be treated with sodium perborate (3 dr to $\frac{1}{2}$ glass of water) as a mouth wash. Gentian violet, 0.5 to 1 per cent aqueous solution, painted on the involved areas, may prove effective. Conant et al suggest gentian violet diluted 1:10,000 in 10 per cent alcohol, painted on involved areas and supplemented by gargling with a 1:100,000 solution of the dye. The gentian violet treatment should be repeated daily for 4 to 5 days and then stopped to avoid irritation of the mucous membrane.

JACOB H SWARTZ

RICKETTSIAL DISEASES

The human infections discussed in this chapter are caused by microorganisms called rickettsiae in honor of H T Ricketts, who first observed these pleomorphic coccobacillary forms and who died of a rickettsial infection acquired in his studies of its etiology.

These diseases occur in man but also occur as parasites of various arthropods and animals. The rickettsial diseases of man are classified into five groups:

- (1) Typhus fever
- (2) Rocky Mountain spotted fever
- (3) Tsutsugamushi disease (scrub typhus)
- (4) Q fever
- (5) Miscellaneous unrelated infections (trench fever, etc.)

The prevention and treatment of the more important infections in the first four groups are considered in this section.

Prevention. THE TYPHUS FEVER GROUP. *Epidemic Louse Borne Typhus.* Recent developments in methods for active immunization of man and for control of human lice have taken this disease from the ranks of the major epidemic scourges of mankind. It is

now possible to produce adequate quantities of potent vaccine in several ways. In the United States Cox vaccine is preferred, it is derived from yolk sacs of developing chick embryos. All persons who are likely to be exposed to epidemic louse-borne typhus should receive a primary course of vaccine consisting of two subcutaneous injections of 1 ml each. The National Institutes of Health of the United States Public Health Service specify the potency which must be attained in epidemic typhus vaccine in the United States.

Evidence from laboratory and field studies clearly indicates that Cox vaccine reduces the mortality of epidemic typhus almost to zero and lessens the severity of the illness, the duration of fever, the number of complications and the period of convalescence. It is probable, moreover, that vaccinated persons are less likely to contract the infection than unvaccinated persons, although this point has not been clearly established. Stimulating doses of 10 ml each should be administered subcutaneously at least twice a year to all persons who are continuously exposed to louse-borne typhus.

Reactions to vaccination against typhus

generally consist of mild local redness of 1 or 2 days duration. In exceptional cases there may be a slight rise in body temperature and malaise with slight headache for 2 or 3 days. It is important to note that the physician must always determine whether his patients are sensitive to egg protein before he administers any type of vaccine derived from chick embryos. A few severe allergic reactions have been recorded and 2 fatalities occurred when egg vaccines were administered to persons with definite histories of sensitivity to egg proteins.

More spectacular than vaccine in its effect in preventing epidemic typhus is the recently developed method for control of human lice. Dichloro diphenyl trichloroethane or DDT is 10 per cent powder in talc or other inert material is lethal to lice. Millions of louse infested persons have been successfully deloused by DDT dust blown into their hair down their necks up their sleeves and into their undergarments either with hand operated dust guns or larger compressed air devices. Clothes which have been properly treated with 10 per cent DDT dust remain lethal for lice as long as a month or more. DDT does not kill the rickettsiae of typhus; consequently every patient with epidemic typhus should be carefully bathed with 1 per cent lysol solution on admission to a hospital and subsequently dusted with 10 per cent DDT powder once a week until discharged. The patient's garments should be disinfected promptly by heat to kill both lice and typhus rickettsiae. All hospital personnel handling typhus cases should be immunized.

gloves in
tient one
infect his
cised in drawing blood; however, since rickettsiae are present in the blood during the febrile period.

Murine Typhus Fever. Although a similar vaccine is available against the relatively mild disease murine typhus fever, its use is recommended only for laboratory or field workers who are continuously exposed to the rickettsiae of murine typhus. In communities where this disease has its highest incidence, the attack rates are not great enough to justify community wide immunization programs. More can be accomplished

by measures to control rats and fleas. The use of 10 per cent DDT dust on rats runs reduces the rat flea population to a low figure and probably also reduces the incidence of murine typhus in man.

Brill's Disease. This mild form of typhus is not known to be associated with lice, fleas or rats. The etiologic agent appears to be closely related to classic epidemic strains of typhus and consequently one might expect epidemic typhus vaccine to have some protective value, but this has not been studied. Since the incidence of the disease is low, the use of vaccine in the attempt to prevent Brill's disease is not justified.

THE ROCKY MOUNTAIN SPOTTED FEVER GROUP. Rocky Mountain Spotted Fever. It is recommended that all persons who plan to visit areas where they may be exposed to infected ticks should be vaccinated with Rocky Mountain spotted fever vaccine prepared either from the tissues of infected ticks or from yolk sac membranes. The potency of these vaccines is regulated by the National Institutes of Health. A primary course of two or three subcutaneous inoculations of 0.5 to 1 ml each should be followed each season by a single stimulating dose. The evidence concerning the use of vaccine over a 20 year period in the Rocky Mountain area clearly indicates its value both in reducing the incidence of Rocky Mountain spotted fever in exposed persons and also in lessening the mortality and clinical severity of the illness. The precautions described in the paragraph

from yolk sacs

Methods for the control of ticks are not satisfactory. DDT is effective against ticks only when excessively large amounts are employed. Risk of contracting Rocky Mountain spotted fever from ticks can be reduced by certain precautions: (1) careful inspection of the entire body twice daily when walking in tick infested areas and prompt removal of any ticks; (2) use of tweezers rather than bare fingers in removing ticks; (3) avoidance of contact with feces or coarsely shed of attached ticks.

Rickettsialpox. This mild illness has been recognized only in New York City but the house mouse and the mite responsible for its

presence occur in many other cities. Preventive measures consist of eliminating house mice.

Recent reviews on the Rocky Mountain spotted fever group have been published by Cov.

TSUTSUGAMUSHI DISEASE GROUP *Tsutsugamushi Disease or Scrub Typhus*. This relatively severe infection has not been recognized in human subjects in North America. During World War II several thousand cases occurred in the United States Armed forces in the South Pacific and in the Burma areas. Attempts to devise a suitable vaccine using the techniques which were successful for epidemic typhus and Rocky Mountain spotted fever have not yielded a satisfactory immunizing agent.

Garments can be impregnated with various materials which effectively repel the mites responsible for transmission of scrub typhus to man. Benzyl benzoate and dibutyl phthalate are the most suitable for this purpose.

Smael has reviewed the recent developments on tsutsugamushi disease.

Q FEVER GROUP The rickettsiae of Q fever have been found in certain ticks and in cows' milk but the various outbreaks of Q fever in man cannot be ascribed to infected ticks or cows' milk. Since the mode of transmission is not understood, relatively little can be done in the prevention of Q fever. Vaccination of experimental animals has been successful but no data are available on the effectiveness of vaccine in human Q fever. This has been shown by Smael.

Treatment GENERAL MEASURES In the care of patients suffering from the more severe rickettsial diseases (epidemic typhus, Rocky Mountain spotted fever and tsutsugamushi disease) several general measures should be observed which may exert considerable influence on the course of the infection. These are briefly considered in the following paragraphs.

Good nursing care is essential. Complete bed rest should be enforced. The patient should be moved in his bed frequently to lessen the hazard of necrosis of the skin. Cold applications may be essential to keep the body temperature from rising above 104° F. The disorientation and stupor which are usually present in severe rickettsial infec-

tions result in a state of helplessness which requires constant attendance by the nursing staff during feeding and elimination. Incontinence of urine is a troublesome complication which may require an indwelling catheter during the acute phase of the disease. The rectal temperature and pulse rates should be recorded at intervals of 4 hours and the blood pressure at least once daily.

The diet should contain 3000 to 4000 calories for an adult with a protein content equivalent to 25 gm of nitrogen for a patient of 150 pounds. For the more seriously ill patient a fluid diet is preferable and in some instances it must be given by tube. Nourishment is best administered in frequent small feedings during the day and once at night. The intake of sodium chloride should be restricted if edema or oliguria occurs.

Fluids should be administered orally or parenterally in amounts adequate to produce a urine output of at least 1500 ml in 24 hours. In patients with high temperatures as much as 4 liters of fluid may be required daily. The fluid intake and output as well as the specific gravity of the urine should be charted daily, particularly in cases with oliguria and/or azotemia. The occurrence of renal failure in a severe rickettsial infection is a bad prognostic sign. A fall in systolic blood pressure below 80 mm Hg may be the first indication that oliguria and azotemia are imminent. When these appear they usually last from 1 to 4 days before the patient either succumbs or the blood pressure rises accompanied by an increase in the urinary volume. The judicious use of intravenous plasma, human albumin or whole blood in this critical period of severe hypotension may be expected to aid the recovery of some patients. The use of intravenous sodium chloride solutions is hazardous for patients with oliguria although the hypotension which accompanies oliguria may be temporarily alleviated by saline infusions. Edema frequently ensues. This is a serious complication associated with a high mortality. In this connection it should be recalled that there usually is a reduction in serum albumin in the acute stage of the more severe rickettsial diseases.

Chloral hydrate or paraldehyde is preferred for the control of active delirium or extreme

restlessness Barbiturates may increase the delirium and should be avoided Relief from headache may be obtained by the administration of codeine in doses of 30 mg at intervals of 3 hours Morphine should be used only with extreme caution in the more severe rickettsial infections Antipyretic drugs are of doubtful value and may be harmful Digitalis preparations are rarely indicated The administration of oxygen may be of value in the treatment of tsutsugamushi disease and should be used whenever patients exhibit cyanosis

To combat the secondary bacterial infections which may occur in severe rickettsial infections antibiotics such as penicillin and streptomycin should be used depending on the sensitivity of the organisms encountered Sulfonamides appear to have an adverse effect on rickettsial infections their use is contraindicated in the acute stage of a rickettsial infection

SPECIFIC THERAPY Before the outbreak of World War II the only specific therapeutic measures for rickettsial diseases which offered any promise were those employing the immune serum of man or animals Beneficial effects were obtained only when the serum was administered in the first 3 or 4 days of the illness Serotherapy now has been supplanted by several chemotherapeutic agents and antibiotics which favorably affect the course of rickettsial infections not only in experimental animals but also in human subjects These various compounds are discussed by Findlay and Snyder This section considers chloramphenicol aureomycin terramycin and para-aminobenzoic acid

Chloramphenicol (Chloromycetin) This antibiotic has given favorable results in the treatment of the various rickettsial diseases Its chemical structure is known and it has been shown to be effective in synthetic form The drug is administered in capsules by mouth The dosage schedule for rickettsial diseases is as follows an initial dose of 40 to 50 mg per kilogram of body weight (this may be divided into three parts and given at hourly intervals) at intervals of 4 hours thereafter a maintenance dose of approximately 10 mg per kilogram until the temperature has been normal for 24 to 48 hours It is not necessary to determine the concentration of the antibiotic in the blood Clinical

improvement usually occurs rapidly and body temperature returns to normal in 36 to 72 hours Chloramphenicol is not toxic in the doses employed No change in red or white blood cells attributable to the antibiotic has been reported

Aureomycin Several clinical trials have indicated the beneficial effects of aureomycin in the various rickettsial diseases The oral route is preferred but the antibiotic is also available for intravenous administration The recommended schedule is an initial dose of 20 to 30 mg per kilogram of body weight, followed by a maintenance dose of 10 mg per kilogram of body weight every 4 hours until the temperature has been normal for 2 or 3 days No important toxic effects have been noted other than gastro-intestinal irritation Clinical improvement usually has been prompt

Terramycin This antibiotic is effective experimentally against the pathogenic rickettsiae and preliminary reports of clinical trials are favorable The dosage is similar to that for aureomycin

Para-aminobenzoic Acid (PABA) This substance is more difficult to administer than the antibiotics mentioned above and does not give beneficial results as promptly Its use is recommended only when the antibiotics are not available Careful attention must be paid to details of administration as emphasized by Snyder and associates

Summary of Specific Therapeutic Agents A direct comparison of chloramphenicol aureomycin and terramycin in human rickettsial infections has not been reported Further clinical evidence is necessary before the physician can logically choose between these antibiotics The evidence available at present suggests that PABA is more difficult to administer properly and less rapid in its action than the antibiotics, but PABA may be used when these are not available

JOHN C SNYDER
ANDREW LEONIAS

REFERENCES

- Bryer M S et al Aureomycin JAMA 138 117 1948
Cox H R The Spotted Fever Group in Rivers T M (Ed) Viral and Rickettsial Infections of Man Philadelphia J B Lippincott Co 1948
Duggar B M et al Aureomycin A New Antibiotic Ann New York Acad Sci 51 175 1948

- Findlay C M The Chemotherapy of Rickettsial Infections *Trop Dis Bull* 45 503 1948
- Pincus M C et al Treatment of Rocky Mountain Spotted Fever with Chloromycetin *Ann Int Med* 28 636 1948
- Ross S et al Aureomycin Therapy of Rocky Mountain Spotted Fever *JAMA* 138 1213, 1948
- Schoenbach E B Personal Communication
- Smadel J E Scrub Typhus in Rivers T M (Ed) *Viral and Rickettsial Infections of Man* Philadelphia J B Lippincott 1948
- Smadel J E Q Fever in Rivers T M (Ed) *Viral and Rickettsial Infections of Man* Philadelphia J B Lippincott 1949
- Smadel J E et al Chloromycetin in the Treatment of Scrub Typhus *Am J for Advancement of Science* 1949 pp 169 177

- Snyder J C The Treatment of the Rickettsial Diseases of Man in *Symposium on Rickettsial Diseases* Am A Advancement Sc, 1948 pp 169-177
- Snyder J C Typhus Fevers in Rivers T M *Viral and Rickettsial Infections of Man* Philadelphia J B Lippincott pp 462-482
- Snyder J C et al Further Observations on the Treatment of Typhus Fever with Para amino-benzose Acid *Ann Int Med* 27 1 1947
- Yeomans A Symptomatology Clinical Course, and Management of Louse borne Typhus Fever in *Symposium on Rickettsial Diseases* Am A Advancement Sc 1948 pp 126-133
- Yeomans A Typhus Fever in the *Oxford Medicine* New York Oxford University Press 1947 Vol 5 p 439

BARTONELLA DISEASE

(OROYA FEVER AND VERRUGA PERUANA)

These two conditions are considered as different manifestations of the same process. Another name is Carrion's disease. It is endemic in South America especially in Peru and Colombia.

In the acute stage or Oroya fever period treatment must be directed toward the rapidly developing anemia. Hodgson has emphasized the importance of frequent transfusions of whole blood and advocates 500 to 700 cc of blood daily during the period of rapid blood destruction. Large doses of penicillin or streptomycin may also be of value in cutting down the incidence of secondary infections. Howe believes that hyperimmune rabbit serum containing a high titer of agglutinins for *Bartonella bacilliformis* may ameliorate the course of the disease but is of no value prophylactically. The dose of the serum is 10 cc intravenously every other day until a total dosage of 50 cc has been administered.

Other than supportive measures there is no other specific form of therapy.

In the chronic or verruga stage excision of the large necrotic nodules may be necessary with careful attention to hemostasis. The prognosis as to life in the chronic stage is excellent whereas the mortality rate in the acute period ranges from 30 to 50 per cent.

FRANKLIN A. LYSEN

REFERENCES

- Craig C F Oroya Fever and Verruga Peruana in *Oxford Medicine* New York Oxford University Press 1947 Vol 5 p 202
- Hodgson C H Treatment of Carrion's Disease with Large Transfusions *Am J Trop Med* 27 69 1947
- Howe C Immune Serum Therapy for Oroya Fever *Arch Int Med* 72 429 1943
- Menesco C Penicillin Therapy in Human Bartonellosis (Carrion's Disease) *J Lab & Clin Med* 30 1021 1945

PROTOZOAN DISEASES

LEPTOSPIROSIS

The treatment of leptospiral infections is unsatisfactory. Fortunately many of them tend to be mild illnesses without jaundice among these are "swamp fever" or marsh fever (*Lept grippotyphosa*) 7 day fever of Japan (*Lept hebdomadis*) 7 day fever of

Australia (*Lept pomona*) and the variously named fevers caused by *Lept bataviae*, *Lept raichman*, *Lept salicem*, *Lept bovis*, *Lept suis*, *Lept felis*, *Lept autumnalis* and others. Illness varies greatly with all strains but that due to *L icterohaemorrhagiae* (Weil's disease) tends to be most severe attended with jaundice in fully half the

cases and with a mortality rate from 4 to 49 per cent Canicola fever (*Lept canicola*) usually pursues a milder course

Treatment of severe leptospirosis due to any species of leptospira is the same as that accorded patients with Weil's disease it is largely symptomatic Dehydration from vomiting is relieved by intravenous liquids containing glucose When possible a high carbohydrate high protein intake is advisable The tendency to bleed may be combated by vitamin K parenterally Transfusions of blood should be given when indicated Sedatives and opiates may be used as required although the severe embarrassment of liver and kidneys should be borne in mind Damage to the kidneys resembles that following hemolytic transfusion reactions hence the oliguria and anuria are doubtless due to the same kind of renal failure recognized in lower nephron ne

anuria have suggested use of lyophilized plasma intravenously High spinal anesthesia has been recommended probably irrationally as an extreme measure to relieve anuria Meningitic symptoms can be relieved only if they arise

Specific treatment includes the use of antibiotics and antisera Penicillin offers just enough promise to warrant its use early and in high dosages Specific antisera have been disappointing in their effects When they are available and suited to the strains responsible they may help in any event the serum should be polyvalent and given early and in large doses 60 cc per day intravenously for 5 days is required Convalescent serum has been warmly advocated as well as transfusions of immune blood but the numbers reported on are small

Other measures have not been proved Streptomycin has been tried in experimental infections with some success although it seems to be weaker than penicillin perhaps combined treatment with penicillin and serum will be in order A recent report by Helman indicates that aureomycin is of definite value in experimental leptospiral infections This drug may prove to be of clinical value after further investigation Many chemicals have been mentioned from time

to time in treatment arsphenamine hexamine sodium tartrobismuthate yatrien and others have all been tried and abandoned The singular resistance of *Leptospira* to the arsenicals antimonials and the current metallic and nonmetallic drugs as well as to the sulfonamides suggests that a new category of drugs especially suited to *Leptospira* must be discovered before leptospiral diseases can be managed

Prophylaxis is important The patients excreta should be sterilized Vaccination with killed *Leptospira* from cultures is recommended in endemic areas Most important is eradication of the rat Contact with rats and with all substances polluted with their urine and feces should be avoided *Leptospira* are able to live freely in the slime of sewers and mines in the waters of canals and swamps and in the gurry of fish wharves Waters need not be visibly polluted to support *Leptospira* hence epidemics among bathers have frequently been reported

HENRY R JACOBS

REFERENCES

- Helman F R Aureomycin in Treatment of Experimental Relapsing Fever and Leptospirosis Icterohaemorrhagica (Weil's Disease) *Proc Staff Meet Mayo Clin* 23 569 1948
Witch Sorgdrager B Leptospirosis *Bull Health Organ League of Nations* 143 1939

MALARIA

Etiology as Related to Treatment The organism responsible for malaria is a protozoan of the class Sporozoa and genus *Plasmodium* There are several species that occur naturally in monkeys birds and reptiles although none of the human species of parasites is known to produce a sustained infection in any of the lower animals Only one species *P knowlesi* a parasite of monkeys has been found by inoculation to be pathogenic to man There are four known species that infect man *P vivax* which causes vivax malaria (tertian benign tertian) *P malariae* which causes quartan malaria *P falciparum* which causes falciparum malaria (malignant tertian estivo-summer) *P ovale* a much rarer species which causes ovale malaria a mild variety clinically similar to vivax malaria

By the bite of an infected mosquito, sporozoites enter the blood stream of man and probably pass through an exo-erythrocytic (cryptozoite) cycle in the macrophages of connective tissue or in the endothelial cells of the liver, spleen, and bone marrow. After this cycle is completed—the length of time depending on the species of plasmodia but usually being less than 10 days—the para-

32 daughter cells are formed, the number depending on the species. During growth, the parasite absorbs the hemoglobin of the red cell, and hemozoin pigment is deposited. A typical malarial paroxysm of chills and fever occurs when the adult parasites rupture the red cell membrane. The free parasites then attack fresh red blood cells. This asexual cycle is repeated at regular intervals—48 hours for *P. vivax*, 72 hours for *P. malariae*, and approximately 36 for *P. falciparum*. After about 10 days of asexual development, the sexual forms, which are known as gametocytes, appear in the blood stream.

Further development of the parasite oc-

way to a female gametocyte, hovering about until one eventually penetrates and fertilization occurs. The unsuccessful ones immediately seek a new mate. The fertilized form, or ookinete, passes between the cells of the mosquito's stomach wall and encysts on its outer surface. Here the sporozoites develop in countless numbers and, on maturity, the cysts rupture and the sporozoites are released in the body cavity of the mosquito. From here they migrate to the salivary gland and await the opportunity to continue their development in the human host following the bite of the infected mosquito. In *vivax* and *falciparum* malaria, the first ring forms appear in the red blood cells of the host 10 to 14 days after the bite of the mosquito. In quartan malaria, the incubation period is longer—18 to 25 days.

Immunology. The immunology of malaria is an important consideration in the therapy of the disease. In animal and human malaria, the immunity of the host is an infection immunity. Once the infection has been completely eradicated, there is only a transient resistance to reinfection. There is relatively little cross immunity between the different species of human malarial infections. Actually, many strains exist within each species of the human malaria parasites that are immunologically distinct or different. Since malaria has a great tendency to relapse, in endemic areas the occurrence of an acute infection after treatment may be either a relapse or a new infection.

The species themselves differ markedly in their immune phenomena. For example, *falciparum* malaria, the most virulent of all types and the one likely to prove fatal if not vigorously treated, has a low relapse rate, in general, probably less than 5 per cent. When a relapse does occur, it is usually within 4 or 5 months following the initial infection and there is rarely more than one relapse. Thirty per cent or more of *vivax* infections, depending on the strain, will relapse in spite of quinine or atabrine. The variety of *vivax* malaria acquired in the Southwest Pacific seems to be the most tenacious yet encountered and 4 years after the end of World War II there remain many relapsing cases, some of which were acquired early in the war.

detected following transfusions since the infected individuals suffer relatively mild or no ill effects from the disease. Practically all cases of malaria which have been reported in the literature 10 or more years after initial infection without opportunity for reinfection in the interim, are proved to be of the quartan variety.

Since the eradication of these infections by chemotherapy does not leave the individual with a permanent immunity, the physician must decide whether it is preferable to attempt a cure or merely to suppress the clinical manifestations of the infection.

One other important point in connection with immunology of malaria concerns vaccines and specific therapy. There is no experimental evidence which indicates that

there will ever be a successful vaccine. Although specific protective antibodies have been demonstrated in experimental animals and man the use of antisera for therapy has not been shown to have any practical value.

Objectives and Principles of Malaria Therapy The selection of drugs or regimens of therapy for the treatment of malaria is dependent on a number of considerations. The most important are the prevalence of malaria in the area, the kind or kinds of species of parasites involved, whether one is dealing with permanent or temporary populations, whether the physician is thinking of the individual or the community, and the potentialities of the different drugs.

The aims of therapy can be classified under the following headings:

(1) Causal prophylaxis or the destruction of the sporozoites injected by the mosquito before they can initiate an infection.

(2) Suppressive therapy. In this instance, the drug is administered to prevent the development of clinical attacks but will not destroy the infection.

(3) Treatment of the acute attack.

(4) Curative therapy.

At the present time it is doubtful if there are any true causal prophylactic drugs that will destroy sporozoites before they undergo development and initiate an infection except in the case of falciparum malaria. In this type, quinacrine, chlorguanide, and perhaps several other drugs if taken in adequate amounts for a sufficient period of time, will serve as true prophylactics.

Suppressive therapy probably will be employed more extensively in the future since the newer compounds are apparently as effective as quinine and quinacrine and are less troublesome to administer. For the individual or for larger groups, such as troops, prisoners, labor forces, suppressive drugs such as chloroquine and camoquin can be given once weekly with complete success. During World War II the writer was responsible for the care of several thousand cases of chronic malaria which were assigned to the hospital because of inability to combat the infection successfully. In one study there were over 500 men suffering relapses at approximately 6 week intervals and a blood survey revealed that over 30 per cent were positive. When they were given 0.6 gm

camoquin weekly, no further relapses occurred and parasites were found only in one individual who had previously had a splenectomy following spontaneous rupture. Large scale studies in the field are currently under way to determine the relative merits of the various suppressive drugs in keeping a community free from clinical malaria and also to learn if transmission of the disease can be interrupted.

The treatment of the acute attack, whether an initial episode or a relapse, usually presents no difficulties. Delayed or inadequate treatment allows some infections to progress until dangerous symptoms appear. Falciparum malaria usually responds promptly to therapy, its reputation for severity results from delay or temporizing. The maxim to follow in the acute attack is to select the drug of choice and to be certain that amounts are given to insure high blood levels as rapidly as possible.

No drugs could be relied on for curative action in chronic malaria until the recent discovery of pentamidine and other 8 amino quinoline compounds. Although further evaluation is necessary, current investigations are extremely promising.

Quinine Quinine has long been the standard remedy for vivax malaria, in fact, its antipyretic qualities have been known for centuries. It is thought that Cinchona bark from which quinine is derived was introduced into Europe about 1640 from South America, where it had been used in the treatment of fevers in general. Supposedly, the name Cinchona was applied to the bark after it had been used to cure the Countess del Chinchon, wife of the governor of Peru of an attack of fever.

As the value of Cinchona bark infusions became known, all readily available sources of the natural bark were soon depleted and this led to the fraudulent substitution of similar appearing inactive compounds. Soon, however, the Dutch transplanted young seedlings to the East Indies where improved horticultural methods and favorable climatic conditions led to the commercial development of high yielding strains. In 1820 the active ingredient was discovered to be in the bark as an alkaloid which could be crystallized. At the present time, there are approximately 20 such alkaloids, all possessing

antimalarial activity but quinine is used almost exclusively because of its high therapeutic effect and low toxicity. It had been the aim of the organic chemists to synthesize this valuable drug but little or no success was obtained until 1944 when Woodward and Doering showed that it could be produced synthetically. The process is so difficult however that it has only academic interest.

Until World War II quinine retained its role as the number 1 antimalarial drug in spite of competition from some of the synthetic compounds such as quinaquine and plasmoquine, which were discovered within recent years.

Quinine is a protoplasmic poison and probably inhibits some of the intracellular enzymes. Some believe that it alters cellular membrane permeability but its exact mode of action is unknown. In malaria there seems to be a direct action on the parasite although when the parasites are mixed with solutions of quinine *in vitro* they can tolerate many times the concentration of quinine possible to obtain in the human body and yet they retain their viability. When given in excessive amounts the drug is toxic producing tinnitus and deafness and if injected intramuscularly it may result in sloughing. Occasionally an individual is found who is sensitive to the action of the cinchona alkaloids but such sensitivity is rare and is easily recognized by the extreme reaction such as cyanosis, dyspnea, urticarial rash, vomiting and fever.

As a treatment for malaria quinine must be considered from two standpoints, namely as a suppressive and as a treatment of the acute attack. It is difficult if not impossible to cure malaria with this compound. Many infections appear to be eradicated following its use although they are usually those strains with a low relapse rate. As a suppressive agent it fails to prevent the acquisition of the infection although clinical symptoms will not appear as long as the drug is used. Quinine perhaps has its greatest usefulness against *falciparum* malaria although it is highly active against all four species of human parasites.

Quinine should be given by mouth in the form of the salt either sulfate or chloride whenever possible. Absorption is rapid and

there is little reason to administer it parenterally except in cases of coma or pernicious vomiting. When given parenterally it should be in the form of the dihydrochloride salt well diluted in saline solution since intravenous solutions if too concentrated, result in thrombosis of the veins.

DOSAGE. Five grams of quinine taken daily by mouth are usually sufficient to prevent the development of clinical symptoms although as stated above quinine will not insure an individual against the development of a subclinical infection.

For the acute attack in adult males the author prefers to use a total of 20 gm of quinine sulfate during the first 24 hours in order to obtain a high concentration of the drug early in the infection. This is to be followed by 5 grains (0.3 gm) three times daily for the next 5 days and then 10 grains (0.6 gm) daily for 2 weeks. The total duration of treatment does not seem to influence the relapse rate. There are many different quinine regimens which are claimed to result in reduced relapse rate although when investigations with adequate controls are substituted no such claims have been substantiated. It has been found that strains and species of parasites respond differently to therapy which accounts for the varying results and claims. In any event therapy should not be discontinued until the patient has had 5 days of normal temperature with negative blood smears.

For undernourished individuals or children the dose can be reduced accordingly. Although quinine is known to stimulate uterine musculature it should be given to pregnant women with malaria since miscarriages are more likely to result from the untreated infection than from the use of quinine. The parenteral dosage should be 10 grains of quinine dihydrochloride in at least 50 cc of saline given slowly. This dosage should be repeated every 4 hours until relief is obtained and the patient is able to tolerate the drug by mouth.

Quinaquine (Atabrine). During World War I the Germans lost their quinine-producing colonies and began vigorous attempts to synthesize an antimalarial compound. This was finally accomplished by Meitzsch and his colleagues in 1930 when quinaquine, a synthetic crystalline dye was discovered to

have potent antimalarial properties. It was introduced into the United States shortly after but never gained popularity until World War II when it was used on a large scale because of the limited supply of quinine.

Quinacrine is an acridine dye and goes under many names throughout the world. Effective against all forms of the malaria parasite, it may be considered comparable to quinine from all standpoints except one. It has relatively little effect on the gametocytes of falciparum malaria. However, it seems to be more effective than quinine as a suppressive drug in this type of malaria. Fairley and his associates in Australia demonstrated that quinacrine, when given prophylactically, prevented the development of falciparum infections. The drug is absorbed rapidly and almost completely from the gastro-intestinal tract. It is degraded slowly, hence it is retained for a long period of time.

DOSAGES When used as a suppressive agent, 0.1 gm of quinacrine per day, taken for 6 successive days, is adequate. For the acute attack, however, it is advisable to give 1 gm of oral quinacrine during the first 24 hours in order to obtain a high level of the drug in the blood stream. This should be given at the rate of 0.2 gm every 5 hours. Thereafter, 0.1 gm three times a day for 7 days is usually sufficient. As in the case of quinine, therapy should not be halted until there has been a minimum of 5 days during which the patient is free from fever and has negative blood smears. The use of quinacrine has several disadvantages. One is the fact that patients become yellow colored as the result of the deposition of the drug in the skin. Another is that many individuals develop gastro-intestinal symptoms. Occasionally a quinacrine psychosis has been reported. This, however, is extremely rare.

If the patient is unable to take the drug orally, it should be administered intramuscularly since the intravenous use occasionally results in collapse. The intramuscular dose is 0.2 gm every 5 hours until 1 gm has been given and then 0.2 gm daily until oral administration can be resumed.

Pamaquin (Plasmochin) Pamaquin is a synthetic 8-amino quinoline compound developed in the German laboratories in 1924. It was highly regarded when first used be-

cause it was thought to reduce the number of relapses. Also it was highly effective as a gametocidal drug. However, it is extremely toxic and can cause methemoglobinemia, cyanosis, vomiting, hemoglobinuria, and even circulatory collapse. Because of the narrow range between therapeutic effectiveness and toxic dosage, its use was discontinued by the armed services during the last war. Pamaquin alone is ineffective for the treatment of the acute attack and, therefore, when used it was usually combined with quinine as a pamaquin compound.

DOSAGE The dosage is $\frac{1}{2}$ grain (0.01 gm) by mouth three times daily for 4 days. When used as a pamaquin compound, the drug is combined with quinine at a ratio of 0.1 gm pamaquin to 1.0 gm of quinine. Since more effective derivatives with less toxic effects have been discovered, the use of pamaquin is not recommended.

Pentaquine An intensive effort was made during World War II to discover a compound which was therapeutically more effective and less toxic than pamaquin. In the 8-amino quinoline group, pentaquine, (8-[5-isopropylaminoamylamino]-1-methoxyquinoline), also known as SN 13,276, has been studied in animals and man for its toxic effects and therapeutic value. There is little doubt but that it is an improved compound in both respects. In experimental animals and in man the pharmacologic activity is similar to that of pamaquin, the drug being rapidly and completely absorbed from the gastro-intestinal tract. Maximal plasma levels are

50 to 75 per cent as toxic as pamaquin but possesses considerably more therapeutic activity. When administered in nearly the maximal tolerated dosage, 120 to 180 mg daily, it has been experimentally demonstrated to be a true causal prophylactic agent in mosquito-induced vivax malaria. South-west Pacific Chesson strain. When used alone in lesser amounts pentaquine will suppress fever and prevent the appearance of parasites in the blood stream, however to prevent relapses it must be used with quinine. Alving and co-workers found that volunteers infected with the Chesson strain of South-west Pacific malaria had a relapse rate of

67 per cent with standard remedies whereas a relapse rate of only 4 per cent was encountered when treatment consisted of 60 mg of pentaquine and 20 gm of quinine daily for 2 weeks. This result is more significant when it is pointed out that the patients were treated at the time of their initial infection or first or second relapse before there was opportunity for the development of specific immunity. All patients were hospitalized since some toxic symptoms occurred with this dosage of pentaquine.

Patients with prolonged malarial infections exhibit considerable specific immunity, a factor of importance when considered from a chemotherapeutic standpoint. Therefore it was thought possible to reduce the dosage of pentaquine by one half and still maintain its therapeutic value. This was proved in 186 ex servicemen who had experienced repeated attacks of malaria many for as long as 5 years. These men had been repeatedly treated with various antimalarial compounds but their infections had not been eliminated. A cure rate in excess of 90 per cent was shown on the initial treatment with pentaquine following a 2 year post treatment period of observation. Proof of cure consisted of absence of relapses in addition to increased body weight and loss of such subjective symptoms as headaches.

The toxic reactions associated with the greater dosage (60 mg) in the experimental studies of Alving were methemoglobin formation and in many subjects anorexia and abdominal cramps. However when pentaquine was used at 30 mg daily there were few or no symptoms of any concern in the ambulatory patients. There was no effect noted on the blood cells. The most frequent subjective complaint was abdominal cramps.

Pentaquine is the drug of choice where curative action is indicated. Its curative value has been demonstrated in acute and chronic vivax malaria. Its value in falciparum and quartan malaria remains to be determined.

RECOMMENDED DOSAGE SCHEDULE AND ADMINISTRATION. For the patient with chronic vivax malaria pentaquine should be administered orally in three divided doses of 10 mg each for 14 days. With each dose of pentaquine 10 grains (0.6 gm) of quinine sulfate should be given for the same period.

If relapses occur the regimen should be repeated. This dosage schedule has been utilized in adults of average size.

When administered to individuals belonging to the dark skinned races vigilance should be exercised in anticipating hemolytic crisis even though this complication may be extremely rare. Signs and symptoms of cinchonism are not to be regarded as indications for withdrawal of the drug unless they are those of a true sensitivity such as rash, cyanosis, etc.

Currently additional 8 amino quinoline compounds are being investigated and preliminary results indicate that a closely related compound may be more active than pentaquine. Available data however are too meager to be recorded.

Chloroquine (SV 7618 and Aralen) and Camoquin (SN 10751). Chloroquine (7-chloro-4-[4-diethylamino-1-methylbutylamino]quinoline) and camoquin (4-[7-chloro-4-quinolylamino]-3-diethylamino-6-cresol) are two synthetic antimalarials developed during the intensive research program conducted under the auspices of the National Research Council in various institutions during World War II. In every respect these compounds seem to be superior to quinine and atabrine when used suppressively or for the termination of the acute attack. A great deal of investigation remains to be done before these drugs can be completely evaluated, but the studies conducted to date have resulted in a consistent demonstration of their superiority. This is particularly true of chloroquine. These drugs are almost completely absorbed by the gastro intestinal tract and toxic symptoms rarely occur in the prescribed dosage. In experimental malaria of lower animals the therapeutic index is much greater than that of quinine or atabrine. In human malaria both chloroquine and camoquin are extremely effective against all species of parasite. The important usage will probably be for suppression since 2 tablets taken once weekly are sufficient to suppress all attacks of malaria even in highly endemic areas. However the rapidity of their action indicates a widespread use for treatment of the clinical attack. It is hoped that the ease of administration and the almost complete freedom from unpleasant symptoms when used in small amounts for suppression would re-

duce the number of effective human carriers so that transmission would not occur. Investigations of this possibility are now being conducted by public health authorities.

DOSAGE The recommended dosage for suppression is 2 tablets each containing 0.25 gm chloroquine diphosphate (equivalent of 0.15 gm of base) taken on the same day of each week. For the acute attack the initial dose is 1.0 gm (4 tablets) to be followed by 0.5 gm (2 tablets) after 6 hours. On the second and third days 0.5 gm (2 tablets) are given making a total of 2.5 gm (10 tablets) in 3 days. Although not necessary 2 tablets can be given daily thereafter for 5 successive days.

Paludrine (Chloroguanide) Paludrine the English proprietary name for a biguanide antimalarial drug 1 (p-chlorophenyl) 4-iso-propylbiguanide was discovered by English workers in 1945. It is a white compound relatively nontoxic. Its chief advantage lies in its apparent wide range between the toxic level and the effective therapeutic dosage. Like quinacrine, quinine and the 4-aminoquinoline compounds the usefulness of paludrine except in *falciparum* malaria is in the suppression or treatment of the acute attack; it has no effect on the relapse rate nor on *P. vivax* or *P. falciparum* gametocytes.

One of the chief disadvantages of paludrine is that it fails to relieve parasitemia or fever as quickly as the drugs discussed above. Magraith reports in some cases the persistence of fever for as long as 4 days after the onset of therapy. In some of the experimental malarial infections particularly galinaceum in birds a high degree of drug resistance was encountered which persisted through mosquito passage. The parasite retained its susceptibility to other antimalarial compounds.

USE AND DOSAGE The author believes that more convincing evidence is needed before this compound can be recommended in preference to the 4-aminoquinoline compounds for suppression or treatment of the acute attack. If used for suppression the recommended dose is 100 mg twice weekly. For the acute attack of vivax malaria 100 mg three times daily should be given for 2 or 3 weeks. Paludrine can be given parenterally in doses of 150 mg intravenously every 4 hours.

Other Antimalarial Agents Methylene blue, arsenic, bismuth, sulfonamides and a few other compounds possess some antimalarial activity. However, when compared with the drugs described above, these compounds cannot be recommended. As stated, convalescent serum known to contain specific antibodies has relatively little effect on the clinical course of the disease.

Supportive Therapy All malaria cases should be kept in bed when possible in spite of the fact that this infection is treated in an ambulatory fashion throughout most of the world. The diet should be light and contain plenty of carbohydrates. Only fluids preferably those containing glucose should be administered during the fever. Fruit juices are beneficial. Patients should be kept warm during the chill and sponge or alcohol baths should be given to relieve high fever. Aspirin 0.6 gm can be given for the severe headaches which, however, usually disappear with rigor. During convalescence iron and liver should be given for anemia. In the uncomplicated cases all nonspecific measures should be directed toward keeping the patient comfortable without overtreatment.

LOWELL T. COGGESHALL

BLACKWATER FEVER

The etiology of blackwater fever, one of the most serious tropical illnesses, remains unsolved. The condition is recognized as a complication of chronic malaria or as being associated with that infection.

Blackwater fever is almost invariably associated with *falciparum* infections. Those reports claiming the vivax malaria parasite as the sole cause lack convincing proof for the absence of *P. falciparum*. The onset of the hemoglobinuria is frequently attributed to quinine. This has never been substantiated but it was noted by Foy in Greece that the high incidence of blackwater fever dropped markedly during World War II when quinine was not available and this was in spite of a marked increase in the number of malaria cases. On the other hand, Foy also reports that Hippocrates gave a precise description of malarial blackwater fever centuries before quinine was used as a medicinal agent. Fairley reported a similar decrease in the incidence of blackwater fever in the Pa-

ific area when quinacrine was substituted for quinine. However, he believed the reduction was associated with the disappearance of falciparum malaria since quinacrine is more effective as a curative compound.

Renal failure is a constant feature of the more severe cases of blackwater fever and relative impairment of function is always present. It is almost certain that the anuria and oliguria are not the result of blockage alone. Undoubtedly renal ischemia plays an important role.

Treatment. The treatment of this disease is that for any individual with sudden hemolysis and impairment of kidney function. It is possible to find innumerable regimens recommended as important in the treatment of blackwater fever. However, when sufficient cases are treated to permit valid evaluation, there is remarkably little difference in the mortality rates. Since there is some suggestive evidence that quinine is detrimental and since there are other drugs equally efficacious if not more so, the use of quinine should be discontinued immediately. Incidentally, parasites frequently are absent from the blood stream during the acute attack. The patient should be kept warm and not moved more than necessary. Nitrogen and chloride balance should be maintained, especially in cases with vomiting. In replacing the loss of blood, no effort should be made to maintain a normal red cell count since the toxemia damages the heart and an excess of blood volume can result in right heart failure. Small frequent transfusions are advisable. Sodium citrate by mouth is recommended, administering 8 gm initially and 4 gm every 2 hours until the urine is alkaline. Sedatives to prevent restlessness are advised, particularly barbiturates.

The prognosis of blackwater fever is all ways grave, the mortality rate averaging about 50 per cent over the world. If recovery is attained, the patient should be removed from malarious areas.

LOWELL T. COGGESHALL

RELAPSING FEVER

(African Tick Fever, Tick Fever,
Spirochæm Fever)

The relapsing fevers due to spirochetes of the genus *Spirochaeta* (*Borrelia*) are similar

clinically, the distinctions based on epidemiologic differences depend perhaps as much on the nutritional state of the patient as on the virulence of the organism. Thus epidemic European relapsing fever, which is louse-borne, tends to be more severe and causes a

tick borne variety is a sporadic disease not associated with social upheaval. However, the species of *Borrelia* involved are dissimilar serologically. Several have been identified: *Bor recurrentis* (European relapsing fever), *Bor duttoni* (tropical relapsing fever), *Bor novyi* and *Bor turicata* (American), *Bor persicum* and others. The tick-borne variety is transmitted to man by the bite of "soft" ticks of the genus *Ornithodoros*. An extraordinary feature is the transmission of the spirochetes through the egg from mother tick to its young, so that the infection may be maintained in ticks alone. Endemic foci may therefore persist without the help of vertebrate infection. The term "tropical" relapsing fever should not divert attention from the fact that endemic foci exist in Arizona, Colorado, Texas, California, Kansas, Oklahoma, and in Canada, and that cases continually appear in those places.

The natural tendency in the majority of cases of relapsing fever of the tick-borne variety is toward spontaneous cure, if the patients are otherwise healthy and strong. Without treatment of any kind, specific or otherwise, the disease runs its relapsing course and then disappears in most instances. A considerable immunity remains after an attack. Nevertheless, desperate illness results from relapsing fever at times. The plan of care of the patient, and the assessment of effectiveness of specific therapy alike, must take into account the importance of the patient's own natural resistance. It is imperative to arrive at diagnosis promptly and to begin specific treatment at the earliest moment because early treatment insures the best outcome. An important part of treatment is the support of the strength of the patient. High fever must be controlled by frequent and thorough sponging. A liberal intake of water must be established. The severe headache should be alleviated by

0.6 gm aspirin given freely and by the use of 30 mg of codeine when required. When the course mounts to a crisis before specific therapy can be started all specific treatment must be withheld to avoid precipitating a fatality. The crisis must be weathered as best it can with help from digitalis, caffeine, morphine, intravenous liquids, ice packs and restraint during delirium.

Neoarsphenamine Neoarsphenamine has been thought specific and curative and although it has proved remarkably effective in numerous cases it fails to eliminate the infection in all according to some workers. Failure has been variously attributed to resistance shown by strains of the organism and to insufficient treatment. Nevertheless neoarsphenamine remains a potent agent. It should be given intravenously in doses of 0.3 to 0.9 gm according to body weight, the total amount required estimated as 0.1 gm per kilogram of body weight. It is best (1) to give the first injection at the beginning of a febrile rise, (2) to give more than one injection, (3) not to give any drug when a crisis is imminent.

The remarkable susceptibility of the spirochetes of relapsing fever to arsenicals and the mildness of the disease in many instances have given rise to the most diverse opinions as to the amount of drug required and how it should be given. Some say that a single dose of 0.03 to 0.5 gm of neoarsphenamine is sufficient to cure 80 per cent of cases; others insist that each case should receive 0.1 gm of neoarsphenamine per kilogram of body weight given in several injections of 0.6 gm each. There are still others who mistrust the curative powers of neoarsphenamine and have resorted to bismuth preparations such as potassium bismuth tartrate or bismuth salicylate. All agree that the arsenicals should be given with care. Severe vomiting frequently follows an intravenous dose. The commonest reaction is exacerbation of the already severe headache and a rise in fever. Sometimes the temperature rises 4 to 7° and the clinical state of the patient deteriorates alarmingly, death during such a reaction is not a rare occurrence. It is especially dangerous to give arsenic to a weakened patient who has already suffered two or more severe febrile cycles. In these patients who obviously need treatment most

urgently, it is best to await the beginning of the next relapse (next febrile cycle) meanwhile supporting the patient by sponging, sedation and adequate water intake and then to begin treatment at the onset of the next episode with a small to moderate dose of neoarsphenamine. Fortunately these patients may now be treated better with penicillin.

The intervals between injections in a course of neoarsphenamine treatment are

give succeeding doses at subsequent febrile onsets whereas others proceed with regular intervals of 3 to 5 days between doses. It seems advisable in the absence of definite evidence to the contrary to attempt a cure with a regular schedule of injections.

In spite of the apparent vulnerability of the spirochetes to neoarsphenamine and mapharsen, cases will occur in which cure is not achieved. Worse still, certain individuals are entirely refractory to arsenicals. In these instances penicillin should be employed.

Penicillin, Penicillin will doubtless attain the dominant position among the drugs useful against relapsing fever as has been noted by Fischer and Taft. It seems a fortunate circumstance that the spirochetal diseases—rat bite fever, syphilis, yaws and relapsing fever—should all yield to penicillin as well as to arsenic so that one or the other of these drugs may be employed at will. Penicillin has a great advantage over arsenic in that it is a safer drug to use. The curative power of penicillin in relapsing fever compares favorably with that of neoarsphenamine. As with the arsenical drugs, treatment with penicillin must be begun with care for the rapid destruction of large numbers of spirochetes may release dangerous amounts of spirochetal products and will invite unnecessary complication from anaphylactoid reactions related to the Herxheimer phenomenon. The caution advised in the use of neoarsphenamine should therefore be exercised with penicillin. The first dose of penicillin should be given at or before the onset of fever; thereafter succeeding doses may follow in regular succession until the projected course has been finished. As with neoarsphenamine, the earlier treatment is begun

the better the outcome. Penicillin may be given intravenously or intramuscularly, ordinarily the intramuscular route is adequate. The literature does not specify how little penicillin will suffice for cure but it seems likely that 30 000 to 50 000 units every 3 hours or comparable amounts of longer acting preparations (procaine penicillin) constitute effective practice and that this be kept up for at least a week. The clinical state and the rate of diminution of the size of the spleen should be considered indexes of progress. It will be wise to continue treatment until cure seems certain and some what beyond so that needless trouble from later relapses is forestalled.

A recent report by Heilman indicates that aureomycin is of value in the treatment of experimental relapsing fever.

HENRY R. JACOBS

REFERENCES

- Fischer I. Penicillin Therapy in Relapsing Fever. Report of Case. *Am J Trop Med* 36:483 1948.
Heilman F. R. Aureomycin in Treatment of Experimental Relapsing Fever and Leptospira Ictero-haemorrhagica (Weil's Disease). *Proc Staff Meet Mayo Clin* 33:589 1948.
Taft W. C. and Pike J. B. Relapsing Fever Report of Sporadic Outbreak Including Treatment with Penicillin. *JAMA* 129:1002 1945.

RAT BITE FEVER

Two distinct diseases are called rat bite fever and have been described in the literature by Witzberger and Cohen, Altmeier et al., Swyer and Wheeler. The first sodoku (cat bite fever) usually is associated with rat bite fever or with the bite of animals that worry rats and is due to *Spirillum minus* (*S. morsus muris*); the second which may follow rat bite but also occurs in epidemic form through contaminated food (Haverhill fever) is due to *Streptobacillus moniliformis* (*Hacterthilla multiformis*, *Actinomyces muris rattis*).

Spirillum minus infections respond well to arsenical drugs. Neoarsphenamine given intravenously in four to six injections of 0.3 to 0.6 gm. is curative in the majority of cases. Mapharsen is also effective. It is necessary to remember that severe reactions may accompany arsenotherapy of this disease, and even though two to three injections are

given it is prudent to administer two or three more to prevent relapse. The first injection should be made at the beginning of a fever cycle. An occasional case will require a course of eight or 10 injections at weekly intervals before it yields and exceptionally arsenotherapy fails altogether. Recently penicillin has been reported on favorably by Altmeier et al. If these early reports are substantiated penicillin will displace the arsenical drugs completely. Apparently the spirilla are susceptible to penicillin for 15 000 to 20 000 units every 3 hours intramuscularly for 5 days is curative.

Streptobacillus moniliformis infections yield readily to penicillin. This is fortunate for they resist all other treatment. A full course of 200 000 to 300 000 units a day for 5 to 7 days is almost certainly adequate and perhaps a less intensive schedule will do.

HENRY R. JACOBS

REFERENCES

- Altmeier W. A., Snyder H. and Howe C. Penicillin Therapy in Rat Bite Fever. *JAMA* 137:370 1945.
Editorial. Rat Bite Fever. *Brit M J* 2:564 1948.
Swyer G. I. M. Rat bite Fever Due to Cat bite. Satisfactory Response to Penicillin after Failure of Arsenotherapy. *Brit M J* 2:380 1945.
Wheeler W. E. Treatment of Rat Bite Fevers with Penicillin. *Am J Dis Child* 69:215 1945.
Witzberger C. M. and Cohen H. G. Rat bite Fever. Comparison of Sporothetol (Sodoku) and the Bacillary (Haverhill Fever) Forms. *Arch Pediat* 61:123 1944.

TOXOPLASMOSIS

Up to the present time no effective agent to combat clinical toxoplasmosis has been discovered. Warren and Sabin have studied the effect of antiprotozoal drugs in experimental animals and found that in mice sulfathiazole has a definitely beneficial effect. Weinman and Bernac have also shown that in acute experimental infections the sulfonamides may be of value but that they have no effect on the carrier state. Because of these laboratory studies sulfathiazole has been used in human cases but the results have been disappointing. Penicillin has been shown to be of no value.

In chronic toxoplasmic chorioretinitis the usual forms of therapy for choroid

should be carried out. Foci of infection must be removed, adequate rest enforced and in well chosen cases induced fever with typhoid vaccine may slow down the inflammatory process.

FRANKLIN A. KAISER

REFERENCES

- Augustine D. L., Weinman D. and McAllister J.: Rapid and Sterilizing Effect of Penicillin Sodium in Experimental Relapsing Fever Infections and Its Ineffectiveness in the Treatment of Trypanosomiasis (*Trypanosoma Lewisii* and *Toxoplasma*) *Science* 99:19, 1944.
- Callahan W. P. Jr., Russell W. D. and Smith M. C.: Human *Toxoplasmosis* *Medicine* 25:343, 1946.
- Warren J. and Sabin A. B.: Effect of Certain Antiprotozoal Drugs on *Toxoplasma* in Vitro and in Vivo *Proc. Soc. Exper. Biol. & Med.* 51:19, 1942.
- Weinman D. and Berne R.: Therapeutic Care of Acute Experimental *Toxoplasmosis* in Animals *JAMA* 124:6, 1944.

LEISHMANIASIS

(Kala-azar, Trypanosomiasis)

Positive diagnosis should be made before treatment is begun and special care should be taken not to mistake the organisms of *Histoplasma capsulatum* for *Leishmania donovani* in bone marrow studies. Treatment of kala-azar makes use of two classes of drugs: (1) organic antimony compounds and (2) diamidine compounds. The antimonials are older and have proved their effectiveness through the years; the diamidines are newcomers which promise great usefulness.

The Antimony Compounds. Tartar emetic is the oldest antimony compound used against kala-azar. It is still employed because of its cheapness. Its toxicity and undependability have stimulated the discovery of more desirable compounds and at present greater reliance is placed upon pentavalent antimonials of lower toxicity and better performance.

Neostibosan (ethyl stibamine, Bayer 693B, von Heyden 693) is the antimonial of choice certainly for the occasional case according to Most and Lavietes. It is the least toxic; it may be given intramuscularly or intravenously and it may be depended on to achieve what an antimonial can in kala-azar. The

initial dose is 0.1 gm dissolved to make a 25 per cent solution given intravenously; the second dose is 0.2 gm and all subsequent doses are 0.3 gm. Injections are given daily or every other day until a total of 45 to 50 gm has been administered. In children depending on their age smaller individual doses are used but the total amount employed should be at least 20 gm. Sometimes cure is not reached under this schedule; treatment should then be continued with doses of 0.3 gm until a total amount of 8 to 10 gm has been given.

Solustibosan (antimony V gluconate antimony hexonate stibatin stibanose stibogluconate) is well regarded by some workers although reports of failures by others will doubtless make this drug seem untrustworthy. It has a low toxicity to recommend it so that large doses may be given intravenously or intramuscularly. Perhaps when a higher dosage schedule is followed solustibosan will become recognized as a dependable preparation. It is supplied in ampules ready for use. Early reports stressed the efficiency with which solustibosan eradicated fever and illness and the rapidity of apparent cure; later ones expressed disappointment over the number of relapses. Vigorous treatment somewhat like that recommended by Sen Gupta and Chakravarty should be employed when solustibosan is used. The total dosage is calculated according to body weight: 4 cc per pound for children, 3 cc per pound for adolescents and 2 cc per pound for adults. Intravenous injections are given daily, not to exceed 10 cc in the child, 15 cc in the adolescent and 20 cc in the adult. The total amount for any person in one course should not exceed 220 cc of the drug. Solustibosan has also been used in an oily suspension given intramuscularly at longer intervals.

Stibosan has been extensively employed by some workers. It is more toxic than neostibosan. A course of treatment comprises 10 to 15 injections of 0.2 gm given intravenously every second or third day. Very ill patients should be started with 0.05 gm and continued with slightly higher amounts according to tolerance. Young children should begin with 0.025 gm per dose, increased slowly to 0.1 gm; adolescents may be started with 0.15 gm, increased to 0.2 gm per dose.

Stibosan is effective but its capacity to produce anaphylactoid reactions makes it less desirable than neostibosan and solustibosan.

Urea stibamine (stiburea) has been popular in India. Although it is an effective drug it is unstable. Furthermore its antimony content and hence its toxicity varies. Its important advantage is that it is inexpensive which makes it useful in mass treatment. The standard dosage is 20 to 25 gm given intravenously every 2 to 3 days beginning with 0.05 gm per dose and increasing by 0.05 gm each time until 0.2 to 0.4 gm is given per injection. A course of treatment requires a month or longer.

Neostam (stibamine glucoside) is given intravenously every other day beginning with 0.2 gm and continuing with 0.3 gm until 15 doses have been given.

The choice of antimonial to be used depends on several factors. When cost may be ignored the best to be had is neostibosan (or solustibosan) because of its low toxicity and dependable effectiveness and because it has few peculiarities of behavior. Other members of the group are also effective but they are better left to persons of large experience or reserved for special situations. A late arrival among the antimonials anthiomaline has been reported upon favorably. When expense is the determining factor in the choice urea stibamine and tartar emetic will have to be used. The use of antimonials is attended with risk of death to the patient in some series a death rate during treatment of 5 per cent has been reported. Certainly fatalities cannot be ascribed to the drug in every case but the implication is plain when neostibosan consistently holds the lowest death rate. The first danger is that due to idiosyncrasy of the patient and this should be tested for carefully at the outset. The second is due to anaphylactoid reactions shortly following injections these reactions are especially common after tartar emetic. A third resembles anaphylactic shock and it appears after injections late in the course of treatment. When a course is finished jaundice may develop. The antimonials should therefore be used with care certainly the least dangerous drug that can be afforded should be chosen. Giddiness and nausea alone shortly after an injection espe-

cially of tartar emetic need not be taken too seriously. Patients with pulmonary tuberculosis advanced heart disease nephritis or grave liver diseases should never receive antimony. In these patients if treatment must be given one of the diamidines should be used certainly a trial with stilbamidine or pentamidine may be risked if tuberculosis complicates kala azar.

The Diamidine Compounds. In recent years a group of nonmetallic drugs has been found effective in the treatment of leishmaniasis all are diamidines and those reported upon are stilbamidine, pentamidine, propamidine and phenamidine. Stilbamidine is most effective but pentamidine will doubtless become most popular. The use of stilbamidine invites the risk of producing diamidine stilbene (stilbamidine) neuropathy which is due to damage to the central nervous system most often manifested by anesthesia and paresthesia of the trigeminal nerve areas. Ooster and Fidler cite lesions that have been found in the brains of dogs treated with this drug. Stilbamidine is a

posed to light and air it quickly becomes toxic and dangerous to use. In spite of great pains one may encounter anaphylactoid reactions. These drawbacks make stilbamidine seem a treacherous drug yet because it may be used when antimonials are forbidden or when they have failed it will have a definite use in the treatment of kala azar. Pentamidine and the others of this group are less toxic but also less effective.

Stilbamidine (stilbamide M & B 744) freshly dissolved in newly distilled water is given intravenously in 1 per cent solution every day beginning with 250 mg and increasing to 50 to 75 mg according to tolerance but never more than 1 mg per kilogram of body weight. The injection should be made slowly. The alarming and troublesome reactions yield to adrenalin most of them may be avoided by giving a small dose of adrenalin just before the injection. With careful attention to the preparation of the solution for injection much difficulty can be averted. A course consists of 10 injections although several more may be needed to pro-

duce the desired effect as described by Widner and Haedicke

Pentumidine (pentamidine isethionate) is also supplied by May and Baker Ltd. It has the great advantage over stilbamidine in not being nearly so toxic. The drug is given intravenously in doses of 75 to 100 mg. every day for 12 to 15 days.

The complications of kala azar must be treated specifically whenever possible. Malaria, intestinal worms, dysentery, amebiasis, avitaminosis, and undernutrition should be dealt with adequately. Cancrum oris in children responds well to penicillin parenterally and to mild local measures during antimony treatment. Sepsis due to bacteria must be combated vigorously with penicillin, streptomycin and sulfadiazine. Complications arising from antimony itself usually subside when treatment is stopped. The frightening anaphylactoid phenomena respond well to adrenalin, but once they appear treatment should stop. If tartar emetic or urea stibamine was responsible, further treatment with neostibosan may be possible.

Treatment of kala azar should continue until clinical and histologic cure is reached. In India kala azar seems to respond better to treatment than it does in Africa, according to reports, but resistant and relapsing cases will appear in any series.

Dermal Leishmaniasis. Three clinical varieties of cutaneous leishmaniasis can be distinguished: (1) post kala azar dermal leishmaniasis, often regarded as a benign outcome of kala azar, (2) oriental sore, or eastern cutaneous leishmaniasis, (3) western cutaneous leishmaniasis, or mucocutaneous leishmaniasis.

Oriental sore usually heals by itself. In any event it runs a mild course without danger to the patient except when unusual complications appear. When a single sore is present it may be treated locally with berberine sulfate in 2 per cent solution injected under and around the ulcer. *Atabrine* similarly given has been credited with rapid cures. Local applications of tartar emetic, sulfa drugs, and penicillin have been recommended. The sores should be kept clean and protected with bandages for they may be

infected by flies carrying the agents of phagedenic ulcer, and sepsis. In addition to local measures, a course of neosti-

bosan given in the manner described for kala azar may prove helpful.

Western mucocutaneous leishmaniasis is another matter. This disease (forest jaw, *espundia*, uta, Chiclero ulcer) may attack the mucous membranes of the nose, mouth and pharynx with the production of painful eroding ulcers causing great deformity and debility. Effective treatment is therefore more urgent than in the other varieties of dermal leishmaniasis. The antimonials are employed much as they are in kala azar. More recently fuadin (stibophen), a trivalent antimonial, has gained preference over the pentavalent compounds. Fuadin is given intramuscularly in courses of 15 to 25 injections, twice a week in doses beginning with 0.5 cc. and increasing to 5.0 cc. When necessary, fuadin may be given every other day in the same amounts.

Organic arsenic compounds such as di-*oxydiaminoarsenobenzol* (*Eparseno*) or *neoarsphenamine*, are also helpful in *espundia*. Local treatment of lesions on the mucous membranes is important because bacterial activity contributes to the destruction. The ulcers should be cleansed twice daily with mild antiseptic washes. Penicillin locally and parenterally should be used when required. Each ulcer should be anesthetized with cocaine solution and coated with powdered potassium antimony tartrate and bandaged. Some physicians recommend injecting emetine hydrochloride in 2 to 5 per cent solution around and under the ulcers, daily for 4 to 5 days, being careful not to use more than 60 to 75 mg. of emetine per day. Berberine sulfate in 1 to 2 per cent solution may be used instead. The outlook for cure is good.

use in prophylaxis

HENRY R. JACOBS

REFERENCES

- Editorial. Kala azar. *J.A.M.A.*, 136:472, 1948.
 Most, H. and Lavietes, P. H. Kala azar in American Military Personnel. Report of 30 Cases. *Medicine*, 26:221, 1947.
 Ostler, E. G., and Fidler, H. K. Cerebral Lesions Produced in Healthy Dogs by the Intravenous

- Injection of 4 4 Diamidino Stilbene *Tr Roy Soc Trop Med & Hyg* 39 533 1946
- Sen Gupta P C and Chakravarty N K Treatment of Kala azar with Sodium Antimony v Gluconate Preliminary Observations *Indian M Ga* 80 560 1945
- Wilner P R and Haedcke T A Relapsing Kala azar Report of Case with Cure Effected by Stilbamidine *New England J Med* 239 250 1948

AFRICAN TRYPANOSOMIASIS

(African Sleeping Sickness)

Before beginning specific treatment of sleeping sickness coexistent diseases and undernutrition should be dealt with when ever possible so that the patient may better endure the potent drugs to be given him

Bayer 205 (germanin suramin belganyl moranyl Fournau 309 antrypol maphuride) is a white stable powder readily soluble in water It is injected intravenously in doses of 10 gm dissolved in 10 cc of water once a week until 100 gm have been given Owing to the remarkable capacity of trypanosomes to become resistant to the drug many workers prefer the doses at shorter intervals The drug is well tolerated but the urine should be examined repeatedly to detect early damage to the kidneys A first test dose of 0.3 gm should be employed to detect idiosyncrasy

Tryparsamide (orsanine Fournau 270) is the drug that must be used after the trypanosomes have entered the central nervous system It is given intravenously in 1 to 4 gm doses in courses of 10 to 15 weekly injections the total amount of the drug for a course being 0.045 gm per kilogram of body weight Treatment should be pushed to the limit of safety because trypanosomes acquire resistance to arsenicals with comparative ease An interval of 2 to 3 months of rest may be followed by a second course if cure was not achieved in the first attempt

Combined treatment is usually recommended A preliminary course of Bayer 205 followed by a course of tryparsamide after 2 to 3 weeks rest Whenever tryparsamide is employed attention should be paid to the eyes because optic neuritis and blindness threaten susceptible patients Unfortunately the most careful watching may not avert disaster since signs of damage might not appear until after treatment is finished Premonitory

symptoms are dimness of vision pain lacrimation and photophobia

Recently the diamidines stilbamidine, pentamidine and propamidine have attracted favorable attention Stilbamidine appears to be less valuable than pentamidine and propamidine Pentamidine isethionate is given intravenously in 8 to 12 doses of 50 to 100 mg each propamidine isethionate likewise in doses of 50 to 75 mg each Both are effective in early cases These diamidines are also useful in prophylaxis 50 mg of either drug per kilogram of body weight intramuscularly in a single dose protects against the disease for 5 to 12 months according to van Hoof et al The diamidines may be used in combination with tryparsamide Harding has reported his experience with 2713 cases treated with the drugs described

HENRY R JACOBS

REFERENCES

- Harding R D Late Results of Treatment of Sleeping Sickness in Sierra Leone by Antrypol Tryparsamide Pentamidine and Propamidine Singly and in Various Combinations *Tr Roy Soc Trop Med & Hyg* 39 99 1945
- van Hoof L et al Chemoprophylaxis of Sleeping Sickness by Pentamidine *Ann Soc belge de méd trop* 26 371 1946

SOUTH AMERICAN TRYPANOSOMIASIS

(Chagas Disease)

Unless penicillin proves to be useful the chemotherapy of Chagas disease will remain unsatisfactory Hitherto specific treatment has made use of Bayer 7602 (AC) or the British preparation M 3024 of the same drug said to be diallyl malonyl di (-4 amino 2 methyl quinonyl 6 amide) which has been described by Fulton This drug is given intramuscularly every 5 to 7 days in doses of 8 to 12 mg per kilogram of body weight Great improvement has been reported from its use but because the course of the disease is frequently erratic amelioration may not have been due to treatment alone Recently

during 2 days

sc
w

reported on The remarkable cardiotropism of *Schizotrypanum cruzi* results in acute or chronic myocarditis which frequently becomes fatal Myxedema from destruction of thyroid gland tissue may be treated with thyroid extract

Prophylaxis requires eradication of the bug vector by sprays of gammaxane DDT or pyrethrum and improvement of housing to make habitations bug proof

HENRY R JACOBS

REFERENCES

- Earle A V Penicillin in Chagas's Disease with Note on Chagas's Disease in Ecuador *J Trop Med & Hyg* 49 74 1946
Fulton J D Comparison of Biological Action of Bayer 7602 (AC) and Corresponding ICI Synthetic Product *Ann Trop Med* 37 164 1943

GRANULOMA INGUINALE

Granuloma inguinale is best treated early as described by Greenblatt Robinson and Marshak and Rodriguez Certain diagnosis rests upon finding the pathognomonic Donovan bodies in the lesions of the disease and since the measure of success of treatment and the test of cure depend alike on microscopic examination of specific material it is prudent to apply skill in the technic in this art Formerly specific treatment depended almost exclusively on the antimonials fortunately streptomycin has been found to be more effective, certainly in production of immediate results and recent evidence indicates that aureomycin may become the treatment of choice Success is more certain with an early start

Antimonials The antimony compounds bring quick results in early granuloma inguinale Tartar emetic is the oldest of this group of drugs It is given intravenously in 1 per cent solution every 2 or 3 days in ascending doses The first dose is 1 cc (A much smaller test dose should be given first to forestall trouble due to idiosyncrasy) Each succeeding dose is 1 cc larger until 10 cc are reached then the dosage is decreased by 1 cc each time until only 1 cc is given Following a rest period of 2 weeks the whole course of treatment is repeated Freshly prepared solutions are preferred to older ones The toxic manifestations of anti-

mony medication such as nausea and vomiting shortly after administration sore gums joint pains anorexia and malaise throughout the course appear frequently and may become severe

Fuadin is more acceptable than tartar emetic It is given intramuscularly only It is available in ampules and is stable The first dose is 15 to 30 cc The second dose is 50 cc 2 days later Thereafter 50 cc are given three times a week until 40 cc have been given in all The injections cause little pain and toxic reactions are uncommon

Anthiomaline is another antimonial that has been used with success It also comes in ampules and is stable It is given intramuscularly three times a week in 3 cc doses

In any event treatment should be continued until healing is complete and satisfactory After healing has taken place weekly doses should be continued for 6 months to prevent recurrences

Other antimony preparations are available for use in granuloma inguinale although they have had less application than the three mentioned above Antimony sodium thioglycollate antimony thioglycollamide and duramin have been used Of the three Greenblatt et al claim that duramin will probably become most popular In general the antimonials produce their best effects when given early in the disease In spite of intensive treatment however certain cases become resistant especially to tartar emetic in some further progress may be made through use of fuadin anthiomaline or duramin and a cure may be achieved After the disease has become chronic the likelihood of cure through chemotherapy lessens

When a stubborn case is found a search should be made for Vincent's organisms in the lesions This complication should be removed by local application of neosporine mine after cleansing the lesions with hydrogen peroxide and by giving hot sitz baths and by applying 20 per cent podophyllin in olive oil daily until the granulations disappear Local anesthetics are applied first if this treatment is too painful Scarlet red ointment should then be em-

ployed to stimulate healing. This regimen is recommended for all cases by Tomskey et al. Continued treatment with antimony may then produce added improvement.

Streptomycin Streptomycin has introduced a new and hopeful departure in the specific treatment of granuloma inguinale. The early report of Barton et al. gave evidence of its effectiveness; this was soon followed by publications by Kupperman, Greenblatt and Dienst who reported almost immediate relief of pain, early disappearance of the Donovan bodies and complete involution of lesions. These authors found that 4 gm of streptomycin per day for 5 days is definitely better than 2 gm per day for a longer period. Hence it is advisable to adhere to the heavier dosage schedule at present. With 4 gm a day and a 5 day course only 1 of 51 patients required retreatment, whereas with 2 gm per day or less for a period averaging 20 days there were 8 recurrences in a group of 32 patients. One patient was given 4 gm a day in vaginal suppositories for 4 days with complete healing. Hursh and Taggart and others have confirmed the curative effect of streptomycin. Penicillin is without effect.

Aureomycin Recently Hill et al. have reported excellent results in the treatment of granuloma inguinale with aureomycin. Twelve cases have been treated successfully. At the start of treatment 300 to 500 mg of aureomycin are administered intravenously two to three times daily for 3 or 4 days. This is usually followed by 50 mg intramuscularly once or twice a day for 10 days. Following this period 250 mg of aureomycin three times daily are given for 10 days.

These authors feel that aureomycin is superior to streptomycin in the treatment of this disease.

Nonspecific Treatment Nonspecific measures designed to hasten cure and applied during specific treatment include surgical excision and raditions with roentgen rays. Excision may be done when lesions are localized. Radiation may be considered when the lesions are extensive; the dosage should be similar to that employed in the treatment of skin cancer and only questionable benefit is to be anticipated. Both measures are important and unless there is assurance that specific therapy cannot achieve cure, either

because of the nature and extent of the lesions or because of their chronicity or resistance they should be postponed.

Each patient is to be urged to return at weekly intervals for at least 6 months after healing seems complete so that the earliest signs of recrudescence will be noted. If streptomycin was used retreatment is in order, if one of the antimonials was used treatment should continue for 6 months with a weekly dose even when nothing is found.

The management of the late effects of granuloma inguinale depends on their nature. Troublesome scars and large keloids may be excised if their removal promises relief.

HENRY R. JACOBS

REFERENCES

- Barton R. L. et al. Granuloma Inguinale Treated with Streptomycin. Report of 3 Cases. *Arch. Dermat. & Syph.* 56:1 1947.
- Greenblatt R. H. Management of Chancroid, Granuloma Inguinale and Lymphogranuloma Venereum in General Practice. *Ven. Dis. Inform.* (supp. 19) pp. 1-43 1943.
- Greenblatt R. H. et al. Treatment of Granuloma Inguinale with Draman. New Antimonial. *J. Ven. Dis. Inform.* 26:238 1945.
- Hill L. M. et al. Aureomycin in Granuloma Inguinale. *J. A. M. A.* 141:1047 1949.
- Hursh H. L. and Taggart S. R. Treatment of Granuloma Inguinale with Streptomycin. *Am. J. Syph. Gonorr. & Ven. Dis.* 32:159 1948.
- Kupperman H. S., Greenblatt R. B. and Dienst H. B. Streptomycin in Therapy of Granuloma Inguinale. *J. A. M. A.* 136:84 1948.
- Marshall L. C. and Rodriguez J. Granuloma Inguinale. Treatment with Streptomycin. *J. A. M. A.* 137:1293 1948.
- Robinson H. M. Jr. Recent Advances in Diagnosis and Treatment of Granuloma Inguinale. *Ann. Int. Med.* 27:1046 1947.
- Tomskey C. C., Vickery G. W. and Getzoff P. L. Successful Treatment of Granuloma Inguinale Treated with Streptomycin. Report of 3 Cases. *Arch. Dermat. & Syph.* 56:1 1947.

SYPHILIS

Syphilis has been known as a disease entity for approximately 450 years. Development in therapeutic agents divides this time roughly into three periods. Therapy until the last 50 years was unsatisfactory and discouraging, but since then advances in the knowledge and treatment of this crippling disease have appeared.

The first period extended from approximately 1493 until the first decade of the 20th century. Therapy in that era consisted mostly of the haphazard use of mercurials, a form of treatment which had been introduced by the Arabs because of the impression that secondary syphilis was a manifestation of scabies. Since both diseases responded somewhat to such medication, little progress was made in differentiating them. During the first part of the 19th century, potassium iodide was introduced and was found to hasten the resolution of some syphilitic lesions.

The second period, which extended from 1903 to 1943, was marked by the discoveries of the etiologic agent of syphilis and a serologic diagnostic test for the disease. In 1905, Schaudinn and Hoffman discovered and described the *Treponema pallidum*, and, in 1907, Wassermann and Bruck applied the complement fixation test to the diagnosis of syphilis. The discovery of the specific etiologic agent opened the field for studies in chemotherapy and, in 1909, Ehrlich and Hata, after the 606th experiment, discovered the chemical preparation salvarsan.

In 1943, the third period began with the introduction, by Mahoney and his associates, of penicillin therapy in syphilis. Because of the wartime economy and all out mobilization of scientific efforts, it was possible to study the effects of this antibiotic to an extent that might never have been possible under ordinary circumstances. The marked advances in treatment made possible the study of other obscure aspects of this protean disease and resulted in the development of many new concepts concerning problems of immunity, infection, and the specificity of serologic tests. From the experiences gained during the past 5 years more concrete opinions have been made on the efficacy of penicillin treatment, especially in the early stages of this disease. Laboratory and clinical investigations in this field are still going on unabated, largely encouraged by early successes, and it is predicted that some new changes in therapy may be at hand before a book can be published. The specific efficacy of penicillin may have on altering the course of syphilis in the latter years of infection is still a matter of conjecture. In this section it is planned to outline spe-

cifically those advances which have resulted from the rapid treatment of syphilis with penicillin. Certain detailed therapeutic regimens will be presented which have proved effective in managing the various stages of syphilis. Throughout this discussion, an attempt will be made to integrate the more recent concepts of immunity since they are most pertinent to the problem of treatment and permit the adoption of more intelligent approach to the management of patients with syphilis. The treatment schedules outlined below represent the collective opinions of most investigators and provide acceptable and effective methods of treatment. No attempt has been made to discuss the various rapid treatment methods which utilize intensive courses of arsenical and bismuth preparations because it is felt that such methods and therapeutic results are readily available elsewhere and have no place in this treatise. The combined use of heavy metals and penicillin will be discussed under the appropriate subheading.

Immunity. The advent of penicillin treatment in syphilis has renewed interest in the problem of immunity to this disease. The specific problems of immunity of great importance in the proper understanding of the fundamental biology of the infection are those concerned with clinical conditions

immunity, as used here, is to be interpreted as meaning "resistance."

NATURAL IMMUNITY. As far as it has been determined, syphilis is a disease which, under natural conditions, occurs only in man. Infections can be produced in certain animals by experimental inoculation and, more recently, it has been shown that other animals, such as mice, rats, guinea pigs, hedge hogs, and hamsters, previously thought to be completely resistant to infection, can harbor the organisms without developing any signs or symptoms of infection.

ACQUIRED IMMUNITY. The development of acquired resistance is dependent entirely on the host's previous experience with the infecting organism. Experiments show, both in animals and man, that following the appear-

ance of the primary lesion a second chancre will not develop ordinarily after a new inoculation with *Treponema pallidum*. This state was called *anergy* as described by Neisser but it is known usually as *chancre immunity*. Such immunity is only relative since reinoculation of massive amounts of infectious material may result in the production of typical primary lesions. The duration of this state of "chancre immunity" is open to a great deal of speculation and it has been demonstrated that patients with late syphilis, general paresis and tabes dorsalis may develop chancres when inoculated with *Treponema pallidum*.

Because of the development of rapid methods of treating syphilis it is now possible to interfere with the development of immunity by the patient at any phase of the disease. This point is extremely important since inadequate therapy results not only in the failure to produce a "cure" but it may interfere with the patient's development of acquired immunity. Such patients are vulnerable to infectious relapses, neurorecurrences and treatment resistant cutaneous and precocious tertiary lesions. At the present time there is no certain method either clinical or laboratory of distinguishing between relapse, reinfection or superinfection in syphilis. With the advent of the rapid method of treatment however a practical point must be considered. If the patient with early syphilis is treated adequately and "cured" but still is permitted to circulate in his previous sexual environment he has an excellent opportunity of becoming reinfectd. Such situations have been noted on numerous occasions and have been designated as *ping pong syphilis*. It is not necessary that the patient develop the characteristic clinical manifestations of syphilis in order to be classified as a case of reinfection. A suspicion of reinfection may arise when the serologic titer increases after therapy.

While all of the above facts are of interest academically and must be considered in interpreting failure rates, a more practical approach must be taken in managing the individual patient. In view of these facts it is most essential that epidemiologic follow-ups be made on all of the patient's suspected sexual partners and the patient himself must be observed carefully for an adequate period of time.

ARTIFICIAL IMMUNIZATION All attempts to produce active immunity by artificial means have been unsuccessful.

MECHANISMS OF IMMUNITY The mechanisms of producing immunity in syphilis remain obscure. No circulating antibodies specific for *Treponema pallidum* have been demonstrated but this does not exclude their existence because virulent strains of *Treponema pallidum* have not been cultivated. There is no doubt that the positive complement fixation and flocculation tests with non

for the positive serologic test may not be the antibodies responsible for immunity. This assumption is based on many animal experiments. However it is felt that certain of the antibodies produced in response to the spiro

propose clinical confirmation of the similarity of these antigens. At this time the serologic titer is at its height and it is assumed that the patient has his greatest acquired resistance owing to the severe clinical manifestations that are noted in his skin and other organs where the spirochetes come to rest.

The recent studies of Neurath and his associates on the flocculation tests for syphilis indicate that there may be a practical method for demonstrating humoral antibodies. By selective chemical precipitating methods they isolated a globulin fraction from the proteins of the blood which carry the antibodies responsible for the serologic test. Either by further refined fractionations or absorption or inhibition activities a more clearly defined picture may arise in relation to the immunology in syphilis.

The cellular factors must play an important part in immunity against syphilis but as in other infectious diseases they cannot be evaluated because they cannot be examined objectively.

CROSS IMMUNITY Clinical evidence indicates that patients with either yaws or syphilis are resistant to both diseases. The degree of cross immunity is largely dependent on factors such as time and the quantities of inoculum used for testing the immunity. However under conditions of natural infec-

tion the degree of cross protection appears to be significant

Serologic Tests for Syphilis Serologic tests are of great value in establishing the diagnosis of syphilis and evaluating the responses of various patients to therapy. Some of the salient features and recent advances made in serologic tests will be pointed out in this section. It is important first of all, to emphasize that nonspecific lipid antigens are used in performing serologic tests for syphilis. In general there are two types of tests: the flocculation and complement fixation. In the flocculation test the antigen is mixed with the patient's serum and the degree of flocculation read directly. The complement fixation test is a more complicated reaction which requires in addition to antigen and serum an accurately measured amount of complement and a suitable hemolytic system. Within the last decade various quantitative procedures have come into greater use in order to give some indication as to the amount of reagin present in the patient's serum. The unit readings vary from laboratory to laboratory. For uniformity therefore all designations will be indicated as dilution units: i.e. the highest dilution giving a reaction of 2 plus or more. Dilution units may be converted to Kahn units by multiplying the former by 4. The quantitative serologic technics have distinct advantages over the qualitative serologic tests, and the following chart indicates the comparative reactions given by the quantitative and the qualitative tests.

QUANTITATIVE VS QUALITATIVE SEROLOGIC TEST FOR SYPHILIS

Quantitative		Qualitative	
Satisfactory fall in titer	256	Dilution Units	Positive
	128	"	"
	64	"	"
	32	"	"
	16	"	"
	8	"	"
	4	"	"
	2	"	"
	1	"	"
			No obvious change

This chart of serologic tests represents a satisfactory fall in titer after therapy and compares it with the qualitative serologic test which shows no change.

The value of such information in managing a syphilitic patient is quite obvious. A progressive increase in serologic titer indicates progression of the disease whereas a steadily falling titer indicates a satisfactory response to therapy. An increase in titer in a patient whose post therapy titer had been falling is a definite indication that the patient has had a relapse or reinfection. Persistently low titered serologic reactions in late latent syphilis adequately treated are indications of a satisfactory course.

Caution must be used in the interpretation of all serologic tests. Such tests are not infallible and are to be considered as only one of the essential aids in arriving at a diagnosis. A single positive reaction by itself is of no significance. If the test fits in with the clinical picture or repeated tests show con-

nosis and treatment

It has become increasingly evident that there are many diseases and febrile states which produce transitorily false positive serologic tests for syphilis. These include such conditions as immunizations (smallpox, typhoid, tetanus, influenza, etc.), respiratory infections (chronic and acute common colds), infectious mononucleosis, malaria, virus pneumonia, bacterial infection, lymphogranuloma venereum, leprosy, and a number of other conditions. Positive serologic reactions with beef heart antigens are obtained also in other treponemal diseases such as yaws, bejel, and pinta, but these reactions are truly positive in the sense that these diseases are elicited by spirochetes which are related morphologically and antigenically to *Treponema pallidum*.

Method of Action of Penicillin in the Treatment of Syphilis

The early studies on the action of penicillin on the organism and the tissues compete for the drug. The combination is completed in a short interval of time, and the death or sur-

vival of the spirochete is dependent on the amount of bound arsenical and the susceptibility of the particular strain of organism to the drug. With penicillin, however, it has been shown that the therapeutic efficacy against the spirochete is enhanced enormously by merely increasing the number of injections. The most striking difference between the action of these two medicaments arises in the fact that it cannot be demonstrated that penicillin is bound and concentrated by the organism. Therefore the treponemocidal action of penicillin can be related to the length of time in which effective spirocheticidal levels can be maintained in the body fluids. Recognition of this time factor and the necessity for maintaining an effective level is most important since it forms the basis for the fundamental differences in therapy with penicillin compared with arsenicals. Eagle and associates have demonstrated that penicillin at extremely low concentrations has a definite spirocheticidal action. They have shown by animal experimentation that the maintenance of blood levels greatly in excess of 0.01 to 0.2 units per cubic centimeter is wasteful of a large part of the active penicillin. Studies on the optimal time interval for the administration of penicillin have yielded variable results. Eagle's experimental work based on the fact that the lag phase of recovery of the spirochetal organism is apparently relatively long indicates that the exact time of each

every 3 hours was adequate for hospitalized patients.

Moore and associates studied the time dosage relationships for amorphous penicillin in patients with clinical syphilis. Their results showed the optimal dose to be 1,200,000 to 4,800,000 units of the drug in aqueous solution and that the total duration of treatment should be between 4 and 15 days. The interval between injections should be within the limits of 2 to 6 hours. Their studies with crystalline penicillin G showed in general that a total of 2,400,000 units of the antibiotic given over a 7½ day period was adequate. When the penicillin was administered in absorption delaying menstrua, a single daily injection of 600,000 units given for a

period of approximately 10 days was as effective as the above schedule employing aqueous crystalline penicillin G. In view of the above noted minimal effective levels and the increasing efficacy of penicillin as a spirocheticidal agent, many of the dosage formulas presented below may seem to be markedly in excess of the necessary dose. Such excesses, however, are on the conservative side and it is felt that they are justified because possibly an increased blood level would favor concentration of penicillin at the site.

It is of most syphilologists that penicillin causes a serious reaction only rarely.

There are four possible types of reactions which may occur during penicillin therapy as follows:

- (1) Toxic actions (primary irritant variety)
- (2) Allergic manifestations
- (3) Therapeutic shock (Jarisch Herxheimer)
- (4) Therapeutic paradox

The chances of a primary toxic reaction resulting from penicillin injections are relatively negligible and have been reported only in patients who have received the antibiotic by the intrathecal method. Since central nervous system syphilis responds satisfactorily to intramuscular injections, there is no necessity of running the risk of a toxic reaction by the intrathecal administration of penicillin.

Mild allergic reactions due to penicillin therapy are not uncommon. It is estimated that they may occur in 8 to 10 per cent of the patients who are treated. The allergic reactions develop most frequently following administration of penicillin in beeswax and oil. The amorphous type of penicillin was much more inclined to produce reactions, probably because of allergenic impurities in the mixture.

Generalized reactions have been encountered in penicillin therapy with symptoms

caria. Skin manifestations may be of the toxic erythema variety or eruptions of the erythematous macular maculopapular and

vesiculobullous types. Urticaria occurs most frequently. Fortunately in most instances the allergic symptoms may be controlled by the use of antihistaminic agents. In patients with dermatophytosis flare ups of the locally infected areas as well as the production or aggravation of id reactions have been noted.

Therapeutic shock or the Jarisch Herxheimer reaction is encountered frequently in the first days of therapy. Approximately 40 per cent of the patients with primary and secondary syphilis will have fever which begins within 12 hours after the start of therapy and continues up to 24 hours. This febrile reaction may or may not be accompanied by an exacerbation of mucocutaneous lesions. Approximately 25 per cent of patients with latent or late syphilis will experience mild febrile reactions to penicillin but in most instances such reactions should not disturb the physician. Jarisch Herxheimer reactions occurring in instances of heavily infected congenital syphilitic infants, syphilitic infections of the upper respiratory tract and perhaps certain cases of cardiovascular and central nervous system syphilis may be serious and in rare instances terminate fatally. It has been noted by some observers that a patient with unsuspected syphilis may develop when injected with penicillin for some other reason a febrile Jarisch Herxheimer reaction as well as a later rise in serologic titer.

Early Syphilis. In the light of current development it is now evident that penicillin alone is the treatment of choice in early syphilis. Two menstrua have been found equally effective for administering penicillin in aqueous solutions and various absorption delaying media. When utilizing crystalline penicillin G in aqueous solution it is agreed generally that a total dosage of 4,800,000 units is adequate. The dosage schedule recommended for the aqueous solution is 50,000 units intramuscularly at intervals of 3 or 3 hours for 96 injections. The first plan requires 8 days and the second 12 days. Clinical evaluation makes it clear that one can accomplish the same end with either the shorter or the longer period and there are advantages in reducing the length of hospital stay.

Therapy of early syphilis on an ambulatory basis now can be accomplished by using

the ne- absorption del- - - - -
in g
is c

aqueous preparation which requires hospitalization. One of the most recent repository preparations is crystalline procaine penicillin G in oil with 2 per cent aluminum monostearate. The latter material is administered in 10 consecutive daily intramuscular injections of 600,000 units each. If possible the injection should be given late in the afternoon at a time when physical activity usually can be kept at a minimum, an important factor in producing a slower absorption of the penicillin.

The modern use of small total doses of arsenic and bismuth concurrently with penicillin therapy has not improved the results with penicillin treatment alone. It is conceivable that results with penicillin might be improved materially by increasing the amounts of arsenical and bismuth used conjointly but the latter type of therapy would defeat the basic principle of rapid treatment and would increase substantially the dangers inherent in arsenic and bismuth therapy. It must be remembered that the use of such agents may produce an anticipated mortality rate of 1/30,000 where for practical purposes there is no danger in using penicillin alone.

Even though penicillin therapy is highly effective against syphilitic infections it does not cure all patients and in order to assure more satisfactory results adequate follow up examinations are necessary. During the first post treatment year the patient should be seen at monthly intervals for physical inspection of the skin and mucous membranes and at each visit a quantitative blood serologic test for syphilis should be obtained. A spinal fluid examination should be done at the end of 6 months if not before. At the end of one year it is advisable to give the patient a complete physical examination and to study the heart and great blood vessels by fluoroscopic examination. During the second year the patient should have a physical examination and quantitative blood serologic test at intervals of 3 months and a spinal fluid examination at the end of the 24 month period. During the third and later years serologic tests should be performed every 3 months for the duration of the patient's life as well as an annual physical examination.

EVALUATION OF RESULTS The aim of treatment has been to secure symptomatic biologic, and serologic "cure." Symptomatic cure is not difficult to accomplish. As a rule, by the end of one year, complete serologic reversal will have been achieved in 80 per cent of the patients. Some 10 to 15 per cent will, at the end of that time, remain weakly sero-positive with a quantitative titer of less than eight dilution units. The persistence of a low serologic titer at the end of one year is not an indication for re-treatment. The determination of biologic cure will require years of observation in each individual patient. When

of penicillin in early syphilis is usually determined by examination of the cumulative failure rates. While the cumulative failure rates vary widely from clinic to clinic it is agreed generally that the composite figures indicate a failure rate for early syphilis ranging between 10 and 15 per cent. There is also some indication that the failure rate is lower in patients who are treated early in the disease.

CRITERIA OF TREATMENT FAILURE The cases of treatment failure can be divided roughly into two groups: (1) those which show manifestations of clinical relapse in addition to increasing serologic titer and (2) those which show only a "serologic relapse." The clinical manifestations include: (a) infectious relapse, (b) ocular relapse, (c) neurorecurrence, (d) birth of a syphilitic baby, and (e) failure of the original clinical syphilitic manifestations to respond to therapy. Serologic relapse can be defined as that state wherein the blood serologic test having reverted to a negative state returns to a positive state, or where the quantitative serologic titer, after falling previously, starts to show persistent rises in titer. In order to make a diagnosis of a serologic relapse, repeated tests should be taken at 5 to 7 day intervals so that the changes noted above can be confirmed definitely. Clinical relapses are seen frequently if serologic relapses are not treated early. Reinfection syphilis may

RETREATMENT When instances of treatment failure are established unequivocally, therapy should be reinstituted. The failure rate for patients requiring re-treatment appears to be slightly higher than the failure rate following the first course of treatment. Crystalline penicillin G in aqueous solution of a total dosage of 9,600,000 units is recommended. The dosage formula should be 50,000 units every 2 or 3 hours for a total of 192 injections. This will require a total of 16 or 24 days to administer. Hospitalization will be required for this type of therapy. For the repository form of crystalline procaine penicillin G in oil with 2 per cent aluminum monostearate, a total of 12,000,000 units will be required. For a period of 20 consecutive days 600,000 units should be given daily. When a second treatment failure is encountered the patient should be given the 26 week arsenic bismuth system, formerly used by the U.S. Army Medical Corps. The following schedule will illustrate the intervals between injection of the various medications.

26 WEEK ARSENIC-BISMUTH SCHEDULE FORMERLY USED BY THE U.S. ARMY MEDICAL CORPS

Week	
1	Bismuth subsalicylate † intramuscularly once weekly, 5 doses
2	
3	
4	
5	
6	
7	omit bismuth for 5 weeks
8	
9	
10	
11	Bismuth subsalicylate intramuscularly once weekly - 6 doses
12	
13	
14	
15	
16	

* Mapharsen dosage. Adjusted approximately to body weight: average dose 60 mg., minimum dose 50 mg., maximum 70 mg.

† Bismuth subsalicylate in oil dosage. The standard dose is 0.2 gm. of bismuth subsalicylate intramuscularly (not 0.2 gm. of elemental bismuth metal).

pect since therapy for both is the same

TWENTY SIX WEEKS SCHEDULE (Cont'd)

17	
18	omit bismuth for
19	5 weeks
20	Mapharsen as in
21	first course twice
22	weekly total 20 in
23	jections
24	Bismuth subsalicylate intramuscularly once weekly
25	5 doses
26	

REACTIONS TO THERAPY Two types of reactions are encountered during the penicillin treatment of the early stage of syphilis. One is the Jarisch Herxheimer reaction, the other is the allergic reaction. There are two types of the Jarisch Herxheimer reaction, one systemic and the other local. The most common systemic reaction is that of elevation of the body temperature following institution of penicillin therapy. Approximately 40 per cent of the patients treated developed a mild febrile Jarisch Herxheimer reaction. The local reaction is characterized usually by an increase in the size of inflammatory reaction of the primary or secondary lesion after institution of therapy. Neither the systemic nor local reactions are of any serious importance except when the lesions are in the nose or throat, or other vital areas where an increase in the size of the lesion could cause a serious embarrassment of a vital function. Adequate precaution for coping with these possibilities should be taken.

Penicillin sensitivity reactions may vary from those of a slight erythema over the body including various urticarial reactions, vesiculous eruptions, etc. to those of generalized exfoliative erythrodermas. Mild sensitivity reactions may be controlled by the use of antihistaminic therapy concurrently with the continued use of penicillin. The more severe reactions warrant, however, the cessation or the temporary withdrawal of therapy.

Late Latent Syphilis Late latent syphilis is an infection of 4 or more years' duration in which the only finding is that of repeatedly positive serologic tests. The diagnosis of this stage of syphilis is based entirely on laboratory results. To establish such a diagnosis definitely the patient should have a normal physical examination, normal fluoro-

scopic examination of the heart and great vessels and a normal cerebrospinal fluid examination. The possibilities of a biologic false positive reaction must be excluded. The decision to treat cases of previously untreated late latent syphilis is based on the desire to prevent development of late complications of syphilis. The state of latency which represents an immediate equilibrium between the host and syphilitic infection implies the possibility of late complication if it remains untreated. Since it is known that about 35 per cent of untreated cases of syphilis will develop late and crippling manifestations, it is felt that therapy in the latent phase is justifiable.

Cases of late latent syphilis treated for a minimum of 6 months with combined arsenical and bismuth therapy present no indications for re-treatment with penicillin. It has been shown that patients with latent syphilis receiving that amount of treatment have a 95 to 98 per cent chance of good clinical health in the future although their serologic test may remain positive in low dilution.

Unlike therapy for early syphilis and the late complications of syphilis, there has been no organized study of treatment results in late latent syphilis. The dosage formulas now being used for late latent syphilis are the same as those used in the treatment of early syphilis. For hospital use, crystalline penicillin G in aqueous solution to a total dosage of 4,800,000 units is recommended. The dosage schedule suggested for the aqueous solution is 50,000 units at 3-hour intervals for 96 intramuscular injections. Completion of therapy will require 12 days.

Therapy of late latent syphilis on an ambulatory basis is probably as effective as treatment in an institution. The regimen recommended is crystalline procaine penicillin G in oil with 2 per cent aluminum monostearate for a total of 6,000,000 units. This should be administered in 10 consecutive daily intramuscular doses of 600,000 units each.

FOLLOW UP PROGRAM The follow-up program for late latent syphilis is necessarily long. Since therapy is prophylactic, it will require 10 to 20 years of observation to determine the efficacy of therapy in the individual case.

It is recommended that the patient have

quantitative serologic tests and physical inspections every 3 months during the first year. If the patient's progress is satisfactory quantitative blood serologic tests every 6 months and a physical examination every year are recommended thereafter. It is advisable to repeat the patient's cerebrospinal fluid examination at the end of 2 years of observation. The yearly physical examination should include fluoroscopic examination of the heart and great blood vessels. These observations should be carried on as long as the patient lives.

EVALUATION OF RESULTS The basic aim of treatment in late latent syphilis is prophylaxis against the development of late complications of syphilis. Many years of observation will be required before any definite conclusions can be drawn concerning the efficiency of penicillin therapy in late latent syphilis.

The reversal of a positive serology to negative is an unsound basis for evaluating the results of therapy. It is important to remember that in infections of more than 5 years duration regardless of type of treatment a persistently positive serologic test is the rule and not the exception. Such patients hereafter will be referred to as seroresistant. The failure of the serologic test to revert to a negative stage is no indication that the results have been unsatisfactory regardless of the degree of improvement in the serologic titer. The probability of eventual clinical progression is not greater in seroresistant patients and is indeed less in those cases whose serologic test for syphilis has reverted to a negative phase after treatment. It is hoped that continued observations will make evaluation of therapy in this stage of syphilis more lucid.

CRITERIA OF TREATMENT FAILURE Treatment failure is indicated by clinical signs and laboratory findings, i.e. the appearance of late complications of syphilis such as neurosyphilis, cardiovascular syphilis, visceral or benign late gummatous syphilis and/or a substantial and persistent increase in the serologic titer.

RE-TREATMENT The therapy proposed for treating serologic relapse is the same as that for retreating cases of treatment failure in early syphilis, doubling the total dose of penicillin and time of administration. Should

re-treatment be required a second time the 28 week schedule formerly used by the U S Army Medical Corps is suggested.

Treatment failures manifested by progression of the syphilitic infection to the late complications should receive more intensive therapy specifically recommended for the particular complication encountered.

REACTION TO THERAPY Reactions to penicillin therapy may occur during the treatment of late latent syphilis as with other stages of syphilis. Therapeutic shock, the Jarisch Herxheimer reaction is encountered less frequently than in the early stages of syphilis. The occurrence of a condition called therapeutic paradox is possible if a syphilitic focus has been overlooked. This end stage is predicated on the assumption that therapy promotes healing so rapidly that scar formation occurs and the vital function of these scarred organs is impaired. The possibility of such an occurrence in properly diagnosed late latent syphilis is extremely small. Therefore under most circumstances it is recommended that the full therapeutic dose be initiated at the start of treatment. If it is impossible to rule out a syphilitic infection in a vital organ it may then be advisable to start therapy with a preparatory regime in the form of smaller doses of penicillin or, in some instances to use preparatory bismuth therapy for 8 to 12 weeks before initiating penicillin therapy. The occurrence of allergic reactions from penicillin therapy may be anticipated in approximately the same frequency as occurs in treatment of earlier stages of syphilis.

Benign Late (Gummatous) and Visceral Syphilis This stage of syphilis may be considered as allergic in type. It is characterized by the occurrence of chronic focal inflammatory lesions involving structures not essential to life or vision in syphilitic infections of 11 or more years duration. The lesions involve the skin or the mucous membrane (late nodular syphilids, cutaneous or mucosal gummas), the bone (periostitis, osteitis, osteomyelitis) or the muscles or tendons (myositis, tenosynovitis). Less

spleen, stomach, and other organs. Gummatous reactions occurring in the vital tissues such as the cardiovascular and cen-

tral nervous system will be discussed later. Benign late gummatous syphilitic lesions are encountered frequently in cardiovascular and central nervous system syphilis.

The mode of action of penicillin in this stage of syphilis is not understood clearly. The beneficial response most probably is due to the direct treponemicidal action of the penicillin. Therapy schedules for benign late syphilis have varied widely but should be predicated on the fact that syphilis, in this stage, still is a generalized disease and should be treated as such. For treatment of hospitalized patients it is recommended that a total of 4 800 000 units of crystalline penicillin G in aqueous solution scheduled in intramuscular doses of 50 000 units at 2 or 3 hour intervals for 96 injections. The period of hospitalization is 8 or 12 days depending on whether the 2 or 3 hour schedule is adopted. Ambulatory therapy, using repository crystalline procaine penicillin G in oil with 2 per cent aluminum monosterate is felt to be adequate. The latter material should be given in 10 consecutive daily intramuscular injections of 600 000 units each.

FOLLOW UP PROGRAM The frequency of follow up visits for patients treated for benign late gummatous syphilis should be influenced by the type of lesions presented. Ordinarily, patients presenting gummatous lesions of the skin, bones and viscera should be observed once a month and observations should be continued until clinical arrest has been secured. Six to 12 months may be required to attain this end point. Thereafter, the patient should be checked quarterly for the next 12 months with particular emphasis on making careful physical examinations and obtaining quantitative serologic tests. A complete evaluation should be carried out after 2 years including physical examination, fluoroscopy of the heart and great blood vessels and cerebrospinal fluid examination. If the patient's progress is satisfactory he should have a physical examination and serologic test annually for the duration of his life.

EVALUATION OF RESULTS Generally, penicillin therapy for gummatous skin, mucous membrane, and bone lesions yields satisfactory clinical results. Statistical results from penicillin therapy for benign late gummatous lesions, exclusive of visceral syphilis, show a

treatment failure rate of 83 per cent. The majority of treatment failures occurred following the use of amorphous penicillin in low total dosages. Penicillin therapy as a diagnostic aid for suspected gummatous lesions should be used with great caution in view of the 83 per cent failure rate.

It is agreed generally that gummatous skin and mucous membrane lesions when treated adequately with penicillin will show healing in less than 3 months. There is little evidence, however, to indicate that the healing rate with penicillin therapy is any more rapid than that obtained under regimens em-

late cutaneous or mucous membrane gummatous syphilis and it is estimated that treatment failures will occur in 5 to 10 per cent.

The number of cases of osseous gummatous syphilis treated with penicillin is comparatively small. It has been shown that uncomplicated periostitis, osteitis, and osteomyelitis will respond satisfactorily to penicillin but cases of syphilitic osteomyelitis accompanied by sequestrum formation or extensive gummatous involvement of the adjacent skin and mucous membranes show less favorable results.

Gummatous visceral syphilis is a relatively rare entity and often it is most difficult to make a clinical diagnosis. The reports on penicillin therapy in visceral syphilis are few in number but in general they indicate satisfactory responses to the antibiotic. The trend of the serologic test in patients with late gummatous stages of syphilis is not a reliable way of evaluating the efficacy of therapy. Statistical analyses reveal that most patients with symptomatic late syphilis maintain positive serologic reactions and that penicillin is no more effective than other forms of syphilotherapy in producing a negative serologic test.

In final analysis it can be stated that approximately 90 per cent of the cases of benign late gummatous syphilis will show satisfactory clinical results after the administration of a single course of penicillin.

CRITERIA OF TREATMENT FAILURE. Treatment failure usually can be detected by

noting the clinical response of the patient

appear. A substantial increase in titer in a patient who previously had maintained a stable serologic titer is definite indication of a treatment failure.

RE-TREATMENT The re-treatment schedules for treatment failure of benign late gummatous and visceral syphilis are the same as those recommended for early syphilis.

REACTION TO THERAPY The febrile sytemic Jarisch Herxheimer reaction is encountered frequently in the therapy of this stage of syphilis and cannot be correlated with any particular type of gummatous lesion.

The possibility of a therapeutic paradoxical in gum involves

nonvital organs. In cases of visceral syphilis the possibility of a therapeutic paradox becomes more pertinent. If the signs of damage are extensive and it is felt that rapid intensive therapy could be detrimental it is suggested that therapy should consist of small initial doses of penicillin or a preparatory course of bismuth injections intramuscularly.

The various allergic manifestations noted previously may occur during penicillin treatment of benign late gummatous and visceral syphilis.

Cardiovascular Syphilis There is considerable controversy concerning the best type of treatment for cardiovascular syphilis and it is extremely difficult to evaluate penicillin therapy in this type of lesion. In fact it is difficult to decide whether or not penicillin therapy does not cause actual harm to the patient. The decision to treat such patients will of necessity be predicated on the careful evaluation of the individual case. Before making a decision concerning therapy the following points should be considered: Does the patient have a moderately good prognosis as to continued life? Will penicillin therapy disturb the delicate balance in the cardiovascular equilibrium of the patient under consideration?

The following facts generally support the

desirability of therapy for cardiovascular syphilis. Statistical studies of necropsy material have shown that in a substantial number of cases the aortas are freed of spirochetal organisms following antisyphilitic therapy. In contrast in those cases that did not receive therapy spirochetal organisms could be demonstrated in their aortas. An evaluation of clinical studies on syphilitic

treated cases observed over long periods of time. Progression to some graver form of the disease occurred in 31 per cent of the untreated cases and only in 19 per cent of the treated cases. If it is kept in mind that the purpose of penicillin therapy is to eradicate the spirochete and not to attempt the restoration of damaged tissue it appears that

that individual patient

Penicillin therapy for cardiovascular syphilis should be carried out on a hospital status. A total of 6 000 000 units of crystalline penicillin G in aqueous solution is recommended. The schedule of administration should be 50 000 units every 3 hours intramuscularly for 120 injections. This amount of therapy will require approximately 15 days to ad-

patient be started with a dosage formula of 1000 units of penicillin at 3 hour intervals intramuscularly for a period of 3 days before instituting the full therapeutic dose.

Appropriate medical measures such as bed rest, digitalis, diuretics, etc. should be used for those cases of cardiovascular syphilis in cardiac failure and antisyphilitic therapy should be withheld until the cardiac status is improved. Antisyphilitic therapy for patients who have had cardiovascular failure should be approached more cautiously. Whenever possible we believe a preparatory course of insoluble bismuth therapy should be given intramuscularly at weekly interval for 8 to 12 weeks before hospitalization or penicillin treatment.

the preparatory

evaluation of the patient's general medical status should be made and penicillin if warranted given in the full dosage formula.

FOLLOW UP PROGRAM Patients with cardiovascular syphilis should be observed at least every 3 months for the first 2 years. At each visit the patient should have a careful general physical examination with emphasis on the

include a cerebrospinal fluid examination. Provided the clinical and laboratory progress is satisfactory semiannual observation usually will be adequate after the second post-treatment year.

EVALUATION OF RESULTS No statistical results are available at this time because no sufficiently large series of cases has been studied. The final determination of efficacy of penicillin therapy in cardiovascular syphilis will depend on prolonged observations of larger groups of cases and on evaluation of the results when compared with groups of untreated control patients and groups treated with heavy metals.

CRITERIA OF TREATMENT FAILURE There are no fixed clinical or laboratory criteria by which improvement in all cases of cardiovascular syphilis treated with penicillin can be measured. Each individual case must be evaluated solely on its own merits. An attempt should be made to differentiate progression of the disease in spite of therapy from the persistence or increase in symptoms due to the residual or progressive anatomic defects already present. The effects of other diseases giving rise to symptoms similar to those caused by the syphilis infection should be differentiated if possible. Serologic tests in this stage of syphilis are notoriously unreliable in evaluating improvement.

RE-TREATMENT The decision to re-treat a patient will depend upon the confirmation of progression of the syphilitic infection or the appearance of manifestations of clinical or serologic relapse. Penicillin is the drug of choice for re-treatment. The schedule recommended is to double the total dose previously given and double the total time of administration.

REACTION TO THERAPY Since the advent of penicillin therapy, controversy has arisen

concerning significance of therapeutic shock and the possibility of therapeutic paradox occurring in cardiovascular syphilis and treatment regimens have been altered frequently in attempts to modify such reactions.

Some feel that there has been too much emphasis placed on the significance of therapeutic shock and/or paradox. It has been demonstrated that 80 per cent of the patients coming to necropsy who have had syphilis for 10 or more years will present evidence of syphilitic aortic involvement. By

syphilis will show no untoward effects. Furthermore, it has been demonstrated by recent study that the Jarisch-Herxheimer reaction may not be altered even though the patient is treated over an extended period of time with preparatory small doses of penicillin. The minimal dose giving no reactions is approximately 500 units per injection. Immediately after the individual therapeutic dose is increased the patient may undergo a typical febrile Jarisch-Herxheimer reaction. Evidence indicates that reactions are as frequent in those cases where therapy is started with small doses as with those begun with the full dosage formula.

Similarly, some observers feel that the so-called therapeutic paradox is the natural sequence of events resulting from the damage of the syphilitic infection on vital tissue and is only secondarily attributable to therapy since it stops the infection and permits fibrosis to occur.

All of these concepts are most interesting and important to those investigators concerned with the problem of treating syphilis. From a practical standpoint, however, it is suggested that each patient be evaluated individually. If the preponderance of evidence indicates that an edematous reaction to treatment or a scarred area may result from therapy, treatment in that patient should be approached more conservatively. The necessary alterations in dosage schedule have been already pointed out.

The usual allergic reactions resulting from penicillin therapy in syphilis also are encountered in the treatment of cardiovascular syphilis.

Syphilis in Pregnancy Over the years syphilis has proved a severe scourge to the pregnant woman desirous of a healthy infant, since the devastating action of the spirochete is greatest in the fetus. The products of conception at times are damaged so severely that they are rejected from the body as stillbirth or a miscarriage. If the fetus survives, the ravages of the syphilitic infection often damage and distort the child's body and many infants have to face life severely handicapped. Before penicillin, therapy was not only tedious but it did not completely insure the delivery of a non-infected infant. Arsenic and bismuth therapy sometimes produced severe reactions in the mother. With the advent of penicillin this situation has been altered drastically, and the outlook for both the syphilitic mother

in G in oil with 2 per cent aluminum monostearate are equally as effective as those with the aqueous solution. The total penicillin dose he recommended was 4,800,000 units. This material is administered in eight consecutive daily intramuscular injections of 600,000 units each.

FOLLOW-UP PROGRAM (MOTHERS) Follow-up observation after penicillin treatment of the syphilitic mother is extremely important because of a few treatment failures. After therapy and until the termination of pregnancy, monthly observations including a careful physical inspection of the skin and mucous membrane and quantitative blood serologic tests are necessary. If suspicious clinical or serologic changes are observed, the patient should be seen more frequently in order to prove the possibility of treatment

of a
syphilis
he 9
the
pregnant syphilitic patient has early syphilis.

The availability of such an effective therapeutic agent for syphilitic infections in pregnancy makes it most important that every effort be made to maintain a high index of suspicion for early diagnosis. It is vital that any cutaneous or mucous membrane lesions occurring during pregnancy be suspected and serologic examinations should be done repeatedly. It is suggested that serologic tests be done at least every 3 months. Such vigilance will help to prevent the patient from coming to term with an unrecognized syphilitic infection.

For all stages of syphilis during pregnancy penicillin is the therapeutic agent of choice. The concurrent use of arsenic and bismuth

tails of such follow up programs can be found under the proper section. It is important to remember that a cerebrospinal fluid examination should be performed as soon after delivery as feasible.

FOLLOW UP EXAMINATION (INFANTS) At the time of delivery a serologic test for syphilis should be made on the cord blood. More important is a darkfield examination of material from the umbilical cord. All infants born of syphilitic mothers should be watched for a minimum of 4 months, regardless of their serologic findings. Follow up visits should be made monthly, including a careful physical examination and quantitative blood serologic tests. Roentgenograms of the infant's long bones should be taken at the first and sixth week of life. The necessity for treating the infant usually can be determined between the second and fourth months of life. Similar observations should be carried out on the seronegative infants of syphilitic mothers. It is important to remember that an infant may acquire syphilis late in gestation or become infected during delivery and thus have a negative serologic test at birth.

Further comments on syphilitic infant follow up will be made under the discussion of congenital syphilis.

EVALUATION OF RESULTS Syphilis in pregnancy has provided the most severe test of the efficacy of penicillin therapy. It is known

suggested schedule utilizing crystalline penicillin G in aqueous solution is 50,000 units every 4 or 3 hours, intramuscularly. Depending on the hours and total amount, administration will require between 8 and 15 days. Penicillin

Ingram's work shows that repository methods using crystalline procaine penicil

evaluation of the patient's general medical status should be made and penicillin if warranted given in the full dosage formula.

FOLLOW UP PROGRAM Patients with cardiovascular syphilis should be observed at least every 3 months for the first 2 years. At each visit the patient should have a careful general physical examination with emphasis on the cardiovascular system including fluoroscopy and a quantitative blood serologic test. The evaluation after 2 years observation should include a cerebrospinal fluid examination. Provided the clinical and laboratory progress is satisfactory semiannual observation usually will be adequate after the second post treatment year.

EVALUATION OF RESULTS No statistical results are available at this time because no sufficiently large series of cases has been studied. The final determination of efficacy of penicillin therapy in cardiovascular syphilis will depend on prolonged observations of larger groups of cases and an evaluation of the results when compared with groups of untreated control patients and groups treated with heavy metals.

CRITERIA OF TREATMENT FAILURE There are no fixed clinical or laboratory criteria by which improvement in all cases of cardiovascular syphilis treated with penicillin can be measured. Each individual case must be evaluated solely on its own merits. An attempt should be made to differentiate progression of the disease in spite of therapy from the persistence or increase in symptoms due to the residual or progressive anatomic defects already present. The effects of other diseases giving rise to symptoms similar to those caused by the syphilis infection should be differentiated if possible. Serologic tests in this stage of syphilis are notoriously unreliable in evaluating improvement.

RE-TREATMENT The decision to re-treat a patient will depend upon the confirmation of progression of the syphilitic infection or the appearance of manifestations of clinical or serologic relapse. Penicillin is the drug of choice for re-treatment. The schedule recommended is to double the total dose previously given and double the total time of treatment.

REACTION TO THERAPY Since the advent of penicillin therapy controversy has arisen

concerning significance of therapeutic shock and the possibility of therapeutic paradox occurring in cardiovascular syphilis and treatment regimes have been altered frequently in attempts to modify such reactions.

Some feel that there has been too much emphasis placed on the significance of therapeutic shock and/or paradox. It has been demonstrated that 80 per cent of the patients coming to necropsy who have had syphilis for 10 or more years will present evidence of syphilitic aortic involvement. By analogy many cases with undiagnosed early syphilitic aortitis treated with the full therapeutic formula of penicillin for latent syphilis will show no untoward effects. Furthermore it has been demonstrated by recent study that the Jarisch Herxheimer reaction may not be altered even though the patient is treated over an extended period of time with preparatory small doses of penicillin. The minimal dose giving no reactions is approximately 500 units per injection immediately after the individual therapeutic dose is increased the patient may undergo a typical febrile Jarisch Herxheimer reaction. Evidence indicates that reactions are as frequent in those cases where therapy is started with small doses as with those begun with the full dosage formula.

Similarly some observers feel that the so-called therapeutic paradox is the natural sequence of events resulting from the damage of the syphilitic infection in vital tissue and is only secondarily attributable to therapy since it stops the infection and permits fibrosis to occur.

All of these concepts are most interesting and important to those investigators concerned with the problem of treating syphilis. From a practical standpoint however it is suggested that each patient be evaluated individually. If the preponderance of evidence indicates that an edematous reaction to treatment or a scarred area may result from therapy, treatment in that patient should be approached more conservatively. The necessary alterations in dosage schedule have been already pointed out.

The usual allergic reactions resulting from penicillin therapy in syphilis also are encountered in the treatment of cardiovascular syphilis.

Syphilis in Pregnancy Over the years syphilis has proved a severe scourge to the pregnant woman desirous of a healthy infant since the devastating action of the spirochete is greatest in the fetus. The products of conception at times are damaged so severely that they are rejected from the body as a stillbirth or a miscarriage. If the fetus survives the ravages of the syphilitic infection often damage and distort the child's body and many infants have to face life severely handicapped. Before penicillin therapy was not only tedious but it did not completely insure the delivery of a non-infected infant. Arsenic and bismuth therapy sometimes produced severe reactions in the mother. With the advent of penicillin this situation has been altered drastically and the outlook for both the syphilitic mother and the fetus are greatly improved.

Pregnancy may occur in any stage of a woman's syphilitic infection and syphilis may be acquired at any time during the 9 month period of gestation. Most often the pregnant syphilitic patient has early syphilis.

The availability of such an effective therapeutic agent for syphilitic infections in pregnancy makes it most important that every effort be made to maintain a high index of suspicion for early diagnosis. It is vital that any cutaneous or mucous membrane lesions occurring during pregnancy be suspected and serologic examinations should be done repeatedly. It is suggested that serologic tests be done at least every 3 months. Such vigilance will help to prevent the patient from coming to term with an unrecognized syphilitic infection.

For all stages of syphilis during pregnancy penicillin is the therapeutic agent of choice. The concurrent use of arsenic and bismuth therapy with penicillin is not recommended. The total amount of penicillin should range between 4 800 000 and 6 000 000 units. The suggested schedule utilizing crystalline penicillin G in aqueous solution is 50 000 units every 2 or 3 hours intramuscularly. Depending on the hours and total amount administration will require between 11 and 15 days. Prior to Ingraham's work on repository penicillin evidence indicated that aqueous solution of penicillin was most effective. Ingraham's work shows that repository methods using crystalline procaine penicillin

in G in oil with 2 per cent aluminum monosterate are equally as effective as those with the aqueous solution. The total penicillin dose he recommended was 4 800 000 units. This material is administered in eight consecutive daily intramuscular injections of 600 000 units each.

FOLLOW UP PROGRAM (MOTHERS) Follow up observation after penicillin treatment of the syphilitic mother is extremely important because of a few treatment failures. After therapy and until the termination of pregnancy monthly observations including a careful physical inspection of the skin and mucous membrane and quantitative blood serologic tests are necessary. If suspicious clinical or serologic changes are observed the patient should be seen more frequently in order to prove the possibility of treatment.

Results of such follow up programs can be found under the proper section. It is important to remember that a cerebrospinal fluid examination should be performed as soon after delivery as feasible.

FOLLOW UP EXAMINATION (INFANTS) At the time of delivery a serologic test for syphilis should be made on the cord blood. More important is a darkfield examination of material from the umbilical cord. All infants born of syphilitic mothers should be watched for a minimum of 4 months regardless of their serologic findings. Follow up visits should be made monthly including a careful physical examination and quantitative

the
the
for
treating the infant usually can be determined between the second and fourth months of life. Similar observations should be carried out on the seronegative infants of syphilitic mothers. It is important to remember that an infant may acquire syphilis late in gestation or become infected during delivery and thus have a negative serologic test at birth.

Further comments on syphilitic infant

nancy has provided the most severe test of the efficacy of penicillin therapy. It is known

that in early untreated infectious syphilis of the mother, there is a 95 per cent risk of infection to the fetus. Composite statistics show that penicillin administered in adequate doses at any time during pregnancy will assure safe delivery of 97 to 99 per cent normal living infants. This remarkable and apparently paradoxical result perhaps can be explained by two factors. The first factor is the ability penicillin has to permeate the placenta from the maternal to the fetal circulation in what are apparently therapeutically effective amounts, even in the very last weeks of pregnancy. The second factor may merely be another indication that a syphilitic infection treated during the incubation period is much more amenable to therapy than after it has become established permanently. Thus with the rapid treatment method utilizing penicillin, the fetus may be treated and in many instances cured while still in utero even though the mother acquires the infection during the latter part of the pregnancy.

The results of penicillin therapy for the mother administered during pregnancy are not materially improved over the results obtained by therapy of syphilis in the nonpregnant adult.

A vital question has arisen regarding the ability of a single adequate course of penicillin therapy to protect the syphilitic mother during subsequent pregnancies. The consensus of nearly all observers is that women in any stage of syphilis who had previously received adequate penicillin therapy or a standard therapeutic regime with arsenic and bismuth either during a previous pregnancy or in a nonpregnant state need not be re-treated during subsequent pregnancies if they continue to maintain a satisfactory clinical and serologic course. This includes those women with adequately treated late latent, seroresistant syphilis. It is advisable, however, to follow all such women with careful observation during subsequent pregnancies. If feasible, the patient should have a careful syphilis survey, including physical examination, fluoroscopy of the heart and great blood vessels, and a cerebrospinal fluid examination before each subsequent pregnancy. During the pregnancy the patient should be checked at monthly intervals by careful physical inspection and quantitative serologic tests.

CRITERIA OF TREATMENT FAILURE The criteria for treatment failure in syphilis in pregnancy are defined clearly. As they are set up they will cover all stages of syphilis that is, primary syphilis, secondary syphilis, infectious relapse, and latent syphilis both early and late. The first criterion is clinical infectious relapse or the failure of the lesions to disappear under adequate penicillin therapy. The second criterion is the failure to show improvement in serologic titer whether accompanied or unaccompanied by clinical manifestations. The serologic titer may fail to decline significantly during a 3 month observation. The serologic relapse may be manifested by a substantial rise in a previously stationary or negative titer. In pregnancy seroresistance is the rule in syphilis of 4 or more years' duration and is not an indication of treatment failure. Reinfection with syphilis may simulate any of the manifestations of treatment failure and for practical purposes should be managed in the same way.

RE TREATMENT Cases of treatment failure in syphilis with pregnancy should be treated according to the schedule outlined under the specific stage of syphilis concerned.

REACTION TO THERAPY Therapeutic shock and the allergic manifestations are encountered in the penicillin treatment of syphilis in pregnancy in approximately the same frequency as found in the same stage of syphilis for the nonpregnant adult. Observations on groups of pregnant women with syphilis treated with penicillin show that the incidence of premature births was 8.8 per cent, as compared with the premature incidence of 7.5 and 10.2 per cent for all births. The consensus of opinion is that penicillin does not predispose to abortion, miscarriage, or prematurity of birth even when the full dosage of penicillin is used initially.

Of all the drugs administered in an attempt to prevent prenatal syphilis, it is felt that penicillin is unevaluated from all phases of observation.

Infantile Congenital Syphilis This group includes syphilitic infections in the infant of 2 years of age or less. The optimal time for treatment of congenital syphilis is *ante partum*, and therapy should be directed toward prevention or cure of the infection in

the fetal stage. In spite of the efficacy of penicillin therapy in prenatal syphilis occasional cases of congenital syphilis may occur.

The postpartum follow up program will usually make it possible to determine whether or not the infant has syphilis by the end of the third or fourth month of life and in many instances prior to that time.

The clinically normal infant at the end of 6 months observation usually may be considered to have escaped infection if the serologic tests are negative. It must be remembered that approximately 20 per cent of infants born of treated syphilitic mothers will still have a positive serologic test at time of birth. Such noninfected infants with a positive serologic test for syphilis usually will develop a negative test by the end of 6 to 8 weeks. If the infant acquires a syphilitic infection just before or during delivery the serologic test usually will be negative at birth but in all probability will become positive during the next 3 to 4 months.

The treatment of choice for infantile congenital syphilis is penicillin. The additional use of small amounts of arsenic and bismuth with penicillin has not added to the efficacy of therapy. Penicillin is preferable because it is a safe agent and can be administered over a relatively short period of time giving an excellent over all cure rate.

The total amount of penicillin to be administered is calculated on the basis of the body weight. It is suggested that crystalline penicillin G in aqueous solution be used. The total amount to be given is calculated on the basis of 200,000 to 400,000 units per kilogram of body weight administered intramuscularly every 2 or 3 hours. The amount of each dose should be calculated in such a way that the whole course will require 8 to 15 days.

No information is available concerning the efficacy of repository penicillin in the treatment of infantile congenital syphilis. Until such information becomes available it is recommended that all patients with infantile congenital syphilis be hospitalized and treated with the crystalline penicillin G in aqueous solution.

FOLLOW UP PROGRAM. The follow up program for cases of penicillin treated congenital syphilis should be similar to that

suggested for adults with early acquired syphilis. Such follow up examinations will reveal early treatment failures if they exist.

The follow up program should include monthly physical examination and quantitative blood serologic tests for a period of 12 months. Patients with osseous congenital

have a cerebrospinal fluid examination approximately 6 months after treatment. The patient should be observed every 3 months during the second year. Complete evaluation should be accomplished at the end of the second year including a physical examination, quantitative blood serologic test and another cerebrospinal fluid study. If response to therapy is satisfactory a semiannual serologic test and an annual physical examination will be sufficient thereafter. The infant should be watched for at least 5 years after therapy and longer periods of follow up may be required if the response to therapy or the stage of syphilis warrants such action.

EVALUATION OF RESULTS. Improvement following penicillin therapy in infantile congenital syphilis is directly proportionate to the age at which the diagnosis is made and therapy instituted. Comparing various penicillin treatment schedules it has been shown that satisfactory clinical and serologic results may vary between 80 and 90 per cent. The clinical manifestations in congenital syphilis at all ages uniformly improve after penicillin therapy. The serologic improvement becomes increasingly less prompt with the duration of the infection and shows a tendency toward stabilization of titer in older infants. Statistics by Neilson and Hanchett show that "serologic cures" were obtained in 100 per cent of their surviving infants treated before the age of 6 months. 54 per cent of cases treated between 6 months and one year and 26 per cent of those cases whose treatment was delayed to the second year. The average time for the serologic reaction to become negative in cases treated within the first 6 months of life is approximately 7 to 8 months after therapy. In the majority of such cases the titers will become negative by the end of 18 months. Positive spinal fluid examinations found early in the infection will tend to show definite improvement 6 to 18 months

after therapy In a similar manner congenital syphilitic infants having bone involvement will show most prompt and rapid response if they are treated in the first 3 to 6 months of the infection Of the infants born with congenital syphilis some are premature or markedly physically debilitated Despite hospitalization and excellent supportive pediatric care in addition to penicillin therapy such infants have a mortality rate of 10 to 12 per cent

Clinical relapse is relatively uncommon in infantile congenital syphilis and is estimated as less than 5 per cent Serologic relapse also is infrequent

CRITERIA OF TREATMENT FAILURE Unsatisfactory response to penicillin therapy in infantile congenital syphilis can be classified in two groups The first group includes those cases which show clinical relapse or progression The second large group consists of those cases in which results of serologic tests are unsatisfactory Platou found that clinical relapses usually occur between the third and 11th month after therapy If the serologic titer fails to decline appreciably or if there is definite indication of a rise in serologic titer a careful survey of the patient should be made in order to determine whether or not any new systems are involved

RE-TREATMENT Treatment failures in infantile congenital syphilis usually will respond to re-treatment with penicillin therapy For re-treatment the maximal dosage weight

in infantile congenital syphilis it was felt by some that the severe systemic and local Jansch Herxheimer reactions occurring in the debilitated or premature infant were to a large degree responsible for the 10 to 12 per cent mortality rate observed during the first 3 to 4 months of life Attempts to reduce this 10 to 12 per cent mortality rate with small doses of penicillin and excellent supportive pediatric care were unsuccessful It is probable that these patients have had their

Late Congenital Syphilis Late congenital syphilis has been defined arbitrarily as a syphilitic infection in children of 2 years of age or older Types of syphilis to be discussed are latent asymptomatic symptomatic visceral osseous and cutaneous

Penicillin therapy is effective in late congenital syphilis The total dosage formula is determined by a weight dosage ratio It is suggested that the patient be hospitalized and crystalline penicillin G in aqueous solution be used There are no results available concerning the efficacy of repository penicillin The optimal total dose is 200 000 to 400 000 units of penicillin per kilogram of body weight The total dose of penicillin should be divided and administered every 2 to 3 hours so that the total therapy will require 8 to 15 days The adult formula should be used for children over 8 years of age when the dosage weight formula calculations give a total dosage greater than 6 000 000 units

hized

REACTION TO THERAPY It has been stated that treatment reactions can be anticipated in approximately 40 to 50 per cent of the penicillin treated cases of infantile congenital syphilis Thirty to 40 per cent develop relatively severe febrile Jansch Herxheimer reactions The local Jansch Herxheimer reactions occur as previously described Allergic manifestations may occur but in most instances the reactions have not been severe enough to require cessation of therapy Antihistaminic therapy is usually beneficial in controlling these allergic reactions due to penicillin therapy

Early in the study of penicillin treatment

titative blood serologic test and a physical examination semiannually for 2 years and should be evaluated annually thereafter

Patients with clinical manifestations should have follow up examinations at monthly intervals until the possibility of treatment

therapy
d as ef
s thera
tion of

therapeutic results is often clouded by anatomic damage done prior to therapy.

The clinical manifestations of late congenital syphilis usually will respond readily to therapy but the rapidity with which improvement is obtained depends on the tissue involved. Liver and splenic enlargement usually will subside slowly over an 18 month period. Cutaneous gummatous lesions usually involute or definitely improve within the

measure of improvement. Drop in the serologic titer usually is slow after treatment and negative tests are attained in approximately 40 per cent of cases observed for as long as two years.

Such irreparable damage may be encountered in late congenital syphilis that no amount of therapy can be effective.

It appears that patients having received previous antiluetic therapy either adequate or inadequate do not respond as well to penicillin as previously untreated cases.

CRITERIA OF TREATMENT FAILURE. Treatment failure either clinical or serologic after penicillin therapy for late congenital syphilis is frequent. When failure is encountered the manifestations are similar to those seen in the various stages of acquired syphilis. Specifically clinical relapse, progression or serologic relapses are found. Serologic relapse has been noted between the fourth and ninth month following treatment. The longer the duration of the syphilitic infection the more frequently are persistently positive serologic tests encountered. Persistently low titered serologic tests are not necessarily an indication of treatment failure.

The appearance of interstitial keratitis in the congenital syphilitic patient treated according to the above regimen must be designated as a treatment failure.

RE-TREATMENT. Therapeutic failures in late congenital syphilis should be re-treated by doubling the total dose of penicillin and the total time of administration. Should penicillin therapy fail the second time a standard heavy metal chemotherapy schedule is recommended.

Progression of the syphilitic infection such as interstitial keratitis or neurosyphilis should

receive re-treatment by the schedule outlined under that specific section.

REACTION TO THERAPY. The Jarisch Herxheimer and the allergic reactions occur after penicillin therapy in late congenital syphilis. The Jarisch Herxheimer reactions are encountered less frequently in late congenital syphilis. The allergic reactions are as frequent in appearance as in other stages of syphilis. Management of the allergic reactions has been previously outlined.

Ocular Syphilis. **SYPHILITIC IRITIS.** Syphilitic iritis is usually a manifestation of late secondary syphilis, seldom occurring before the sixth month of infection and often as late as the second year. Iritis may be associated with early infectious relapse. Iritis constitutes about 73.3 per cent of the total eye complications of early syphilis.

Penicillin is a safe, rapid and effective method of treating syphilitic iritis. Between 4,800,000 and 6,000,000 units of crystalline penicillin G in aqueous solution are recommended. The dosage schedule recommended for aqueous solution is 50,000 units intramuscularly at intervals of 2 to 3 hours for 96 or 120 injections given in 3 to 15 days.

The use of repository penicillin on an ambulatory basis will probably be as effective as the use of aqueous solution. Crystalline procaine penicillin G in oil with 2 per cent aluminum monostearate is one of the most recent preparations. This latter material is given in 10 daily intramuscular injections of 600,000 units each.

Ocular syphilis should be treated con

syphilitic iritis should be the same as that outlined in the section on early syphilis.

For the first treatment failure it is suggested that penicillin be used doubling the total dose and the total time of administration. The therapy suggested for a second treatment failure is the 26 week heavy metal therapy program formerly used by the Medical Corps of the U.S. Army.

Syphilitic iritis uniformly responds well to penicillin therapy. Beneficial effects usually are noted by the second day of treatment and in most cases complete improvement will occur by the 21st day. In nearly all patients the visual acuity will return to normal.

or to that prior to infection. Prolonged infections without concurrent ophthalmologic care frequently will result in permanent visual damage.

Treatment failure may be both clinical and serologic. The iris may show recurrence of the inflammatory process. Infectious relapse such as mucocutaneous and neurologic is encountered and usually will show a prodromal increase in the serologic titer. Similarly serologic relapse may occur alone.

Reactions to penicillin therapy for syphilitic iritis are the same as those seen in other stages of early syphilis. A local Jarisch Herxheimer reaction may be manifested by an aggravation of the ocular inflammation. This local reaction will usually occur during the first day of treatment. Symptoms of photophobia, lacrimation and pain may occur or increase in the inflammatory process and may be demonstrable by use of the corneal microscope and slit lamp.

The allergic reactions to penicillin therapy in syphilitic iritis are those commonly encountered in early syphilis.

INTERSTITIAL KERATITIS. Interstitial keratitis is a common occurrence in congenital syphilis. It has been shown that 52 per cent of all persons brought to medical attention because of congenital syphilis have interstitial keratitis. Interstitial keratitis is rare in secondary syphilis and even after chancres of the eyelid.

The cause of interstitial keratitis is unknown. It is conjectured but not proved that the lesion is in some way due to infection allergy. Interstitial keratitis is seen most frequently between the ages of 5 and 16 years. Patients who are untreated or poorly treated will have residual damage to the vision in an estimated 20 to 40 per cent. The process produces an inflammation of the entire cornea with grayish infiltrates toward the periphery and subsequent vascularization. Severe photophobia, lacrimation and conjunctivitis are the symptoms presented.

Treatment of interstitial keratitis has produced highly variable and unpredictable results. Penicillin therapy alone for interstitial keratitis has been discouraging. It is the gen-

eralized and carefully studied for his ability to tolerate hyperpyrexia.

Six million units of crystalline penicillin G in aqueous solution are recommended. The dosage schedule suggested is 50,000 units intramuscularly at 2 or 3 hour intervals for 120 injections. The first schedule will require 12 days and the second 15 days. Hyperpyrexia should be used concurrently with the penicillin therapy. A temperature above 39.2° C should be maintained for a minimum of 25 hours. For information concerning the type and method of producing artificial hyperpyrexia, the reader is referred to standard textbooks on this subject.

Ambulatory repository penicillin therapy is not recommended in the treatment of interstitial keratitis.

Concurrently with systemic therapy favorable results have been reported using penicillin locally in patients with interstitial keratitis. Penicillin was introduced by iontophoresis, cotton pad soaks and ophthalmic ointment.

Klauder's report indicates that the active interstitial keratitis is not altered specifically by penicillin therapy. It has been shown repeatedly that penicillin therapy does not prevent the initial attack of interstitial keratitis nor will it prevent involvement of the second eye or recurrence in the previously affected eye. Klauder believes fever therapy is still the treatment of choice. Even though penicillin has no advantage over chemotherapy as to results, it is probably the best adjunct treatment for fever.

Therapy for interstitial keratitis is still far from satisfactory.

The follow-up studies for patients with interstitial keratitis are the same as those outlined for the appropriate stage of the accompanying general syphilitic infection. In addition to the usual studies, careful ophthalmologic examinations should be made at each visit, including visual acuity.

One of the most common manifestations of treatment failure is seen frequently after penicillin therapy alone. The serologic reaction in interstitial keratitis is not a reliable means of evaluating treatment failure. It is possible that serologic

relapse will occur after treatment of interstitial keratitis and may be the prodromal

combined penicillin and fever therapy. The penicillin dosage and time of administration should be doubled. Twenty-five hours of fever therapy by an accepted method should be used. For a second treatment failure the 26-week heavy metal therapy program as previously used by the U. S. Army Medical Corps combined with fever therapy is recommended. Fever therapy above the level of 39.2°C at this time should be given in the full therapeutic dose of 40 to 50 hours.

Jarisch-Herxheimer reactions are encountered frequently in penicillin therapy for interstitial keratitis. There have been no indications that penicillin therapy will produce a local Jarisch-Herxheimer reaction involving the cornea.

Allergic manifestations resulting from penicillin therapy also occur during the penicillin treatment of interstitial keratitis.

SYPHILITIC PRIMARY OPTIC ATROPHY
Syphilitic primary optic atrophy is a syndrome characterized by gradually diminishing vision and almost always associated with tabes dorsalis, taboparesis, or general paresis. The syphilitic infection or its toxic products apparently slowly destroy or render nonfunctioning the fibers of the optic nerve. The peripheral portions of the visual fields usually are destroyed first. Earliest diagnostic aids in this syndrome are the occurrence of simple scotomata and a diminution of the visual fields. It is believed that considerable permanent damage will have been done when the clinical symptoms become evident. Early diagnosis and treatment are paramount in preventing loss of vision.

It appears that combined penicillin and fever therapy is the treatment of choice. Hospitalization is recommended. The patient's ability to tolerate hyperpyrexia should be studied. A total dosage of between 6,000,000 and 8,000,000 units of aqueous crystalline penicillin G is recommended. The administration schedule suggested is 50,000 units intramuscularly every 2 or 3 hours for 120 to 160 injections. The complete administration will require between 12 and 20 days. Hyperpyrexia should be induced concur-

rently with the penicillin therapy. A minimum of 25 hours of fever above 39.2°C is felt to be adequate for most patients.

Repository penicillin therapy on an ambulatory status is not considered adequate treatment.

Follow-up studies on patients with syphilitic primary optic atrophy should be the same as those outlined for the accompanying stage of neurosyphilis. In those rare instances where the cerebrospinal fluid is not involved the follow-up studies should be the same as those outlined for tabes dorsalis including visual acuity and visual field examinations.

The evaluation of any form of therapy for primary optic atrophy is obscured by the frequent occurrence of progressive blindness in spite of assumed adequate therapy and laboratory evidence of an arrested general syphilitic infection. The duration of the infection before institution of treatment appears to be an important factor in the ultimate outcome. There is a wide divergence of opinion among observers concerning the effectiveness of therapy in the

to be the optimal therapeutic regimen now available.

Therapeutic results in primary optic atrophy are extremely difficult to evaluate with the present known methods. It is almost impossible to determine whether the progression of clinical symptoms and signs is due to continued activity of the syphilitic process or due to the fibrosis accompanying healing. Study of the spinal fluid will help determine the overall effectiveness of therapy of central nervous system syphilis. Results are not helpful in the therapy of visual acuity and visual fields are only moderately helpful.

Failure of the cerebrospinal fluid to improve after therapy is an indication for re-treatment as with other stages of neurosyphilis.

Evaluation of treatment results must be done on the individual patient basis using all the clinical and laboratory information available

If treatment failure is based on the failure of the cerebrospinal fluid to improve or if it shows reactivation, therapy appropriate for that stage of neurosyphilis is suggested

If the patient becomes progressively blinder during a 6 month period after treatment, it is suggested that treatment be re-introduced using the original formula of 6,000,000 to 8,000,000 units of penicillin and fever therapy above 39.2° C for 25 hours. This is to be administered regardless of the titers obtained or examinations of the cerebrospinal fluid or blood

The febrile Jarisch Herxheimer reaction has been reported in penicillin treatment of primary optic atrophy. Such reactions occur less frequently than in early syphilis

Neurosyphilis Syphilis of the nervous system produces a variety of clinical and pathologic entities. A classification can be made on the basis of the tissue involved and the pathologic responses. The meninges, blood vessels, or parenchyma of the brain usually are attacked. The pathologic reaction may be either inflammatory or degenerative in type. Clinical syndromes have been described because the syphilitic infection produces the same reactions in many patients. All stages of these syndromes are encountered and will mirror the activity of the syphilitic infection or the resultant damage

The changes in the cytologic and chemical components of the cerebrospinal fluid are more reliable than the clinical manifestations for indicating the activity of the syphilitic infection in the neural tissues

Clinically the various syndromes are designated as follows

- (1) Asymptomatic nervous system syphilis
- (2) Diffuse meningovascular syphilis
- (3) Acute syphilitic meningitis
- (4) General paresis
- (5) Tabes dorsalis
- (6) Taboparesis
- (7) Vascular neurosyphilis including thromboses and hemorrhage of the cerebral and spinal vessels
- (8) Gumma of the brain and spinal cord

(9) Syphilitic epilepsy (nonparetic)

(10) Erb's spinal spastic paraplegia

(11) Nerve deafness

SPINAL FLUID EXAMINATION Since the days of Wagner-Jauregg the effects of anti-syphilitic therapy have been measured by alterations produced in the cerebrospinal fluid findings, as well as clinical improvement. Study of the changes in the cerebrospinal fluid components is an objective method of evaluation. The proper evaluation of a cerebrospinal fluid requires (1) a cell count performed immediately after being drawn, (2) quantitative total protein determination, (3) specific quantitative complement fixation test for syphilis, (4) a colloidal protein test either gold or mastic*

The cell count affords the most valuable information as to the immediate activity of the syphilitic infection in the nervous system. A count of more than 5 cells per cubic millimeter is considered evidence of activity. An increase in the total protein determination also indicates activity of the infection or degenerative reaction in the nervous system tissue. The colloidal test utilizing the globulin fraction to a lesser degree indicates activity and tissue destruction. These latter two tests do not change as rapidly as the cell count. The complement fixation reaction for syphilis determines the specificity of the process. The serologic reaction usually is slow to develop and disappears equally as slowly

For complete evaluation of neurosyphilis and its therapy both clinical and laboratory tests must be utilized in individual cases

There appears to be general agreement that penicillin is the drug of choice in neurosyphilitic therapy and has replaced metal chemotherapy. Differences of opinion exist concerning the efficacy of penicillin therapy alone as against combined penicillin and fever therapy. The additional benefit of fever therapy in combination with penicillin is predicated on two facts. (1) It is well known that fever therapy has definite clinical value in the treatment of neurosyphilis, (2) it has been shown experimentally that the spiro-

* We feel that the colloidal protein test is of little value in diagnostic and therapeutic evaluation of syphilis of the central nervous system. However since it is in common use we will indicate the effects of therapy on this test

cheticidal activity of penicillin is enhanced in the presence of temperature elevations. Clinical studies by Dattner show that the

and his associates have found after long term observations that penicillin therapy alone is as effective as combination therapy.

Six million to 10 000 000 units of penicillin are recommended for the treatment of asymptomatic, acute meningeal, diffuse meningovascular, gumma, and vascular neurosyphilis. Utilizing hospital care, aqueous crystalline penicillin G given in a dosage schedule of 50,000 units intramuscularly every 3 hours over a period of 15 to 25 days is recommended. Unpublished information indicates that repository penicillin may be equally as effective as aqueous crystalline penicillin G. A recent preparation is crystalline procaine penicillin G in oil with 2 per cent aluminum monosterate. The ambulatory schedule should be daily intramuscular injections of 600,000 units each for 10 to 17 days.

For the degenerative types of neurosyphilis, such as paresis, tabes dorsalis, and taboparesis, 8 000,000 to 12 000,000 units of penicillin are recommended. The patient should be hospitalized and given 50 000 units of aqueous crystalline penicillin G, intramuscularly every 3 hours for a period of 20 to 30 days.

Ambulatory repository penicillin therapy is not recommended as the treatment of choice for degenerative stages of neurosyphilis.

In individual patients wherein the clinical manifestations warrant and the physical condition will permit, fever therapy can be utilized. It is suggested that hyperpyrexia be induced by the standard method, maintaining the fever above 39.2°C for a minimum of 25 hours but preferably 50 hours. The decision to use fever therapy should rest upon the merits of the individual case.

FOLLOW UP PROGRAM The following standard program is suggested as a basis for evaluating penicillin-treated neurosyphilitic patients. The first year after treatment observations should be made every 3 months. Semiannual examinations should be made thereafter for the next 4 years. After 5 years

annual evaluations will be adequate if the patient's progress is satisfactory. Lifetime observation is advisable. These follow up observations should include an interval note, physical examination, quantitative blood serologic test, and a cerebrospinal fluid examination. Each cerebrospinal fluid sample should be subjected to a cell count, quantitative total protein determination, colloidal protein test (gold or mastic), and a complement fixation test. Special emphasis should be placed on examination of the patient's mental status and nervous system, by a psychiatrist if possible.

EVALUATION OF RESULTS To evaluate properly the efficacy of penicillin therapy in neurosyphilis both the clinical and laboratory findings must be considered. The clinical findings are more difficult to interpret since some of the symptoms and signs may be due to permanently damaged or destroyed tissue.

Changes in the cerebrospinal fluid components are an objective method of studying activity of the syphilitic infection. The Dattner-Thomas concept of spinal fluid activity is the presently accepted standard of measurement. Briefly this concept states that if therapy has been successful there will be a progressive reduction in the cerebrospinal fluid cell count and protein content toward normal. Over a longer period the colloidal protein test (gold or mastic) and the spinal fluid complement fixation test for syphilis will revert to negative. The cerebrospinal fluid may be rendered inactive, unassociated with definite clinical improvement. The clinical evaluation of response to penicillin therapy in the neurosyphilitic patient is more difficult. In order to provide a basis of comparison, pre and post penicillin therapy, all symptoms and signs need to be studied objectively. A careful history and physical ex-

spinal cord, or peripheral nerves.

According to Moore, results of penicillin-

paresis—increased cell counts in the spinal fluid promptly become normal sometimes within a few days even during the period of treatment but practically always within 60 days. The elevated protein content in the cerebrospinal fluid likewise becomes normal in a period of 2 to 3 months. Colloidal protein (mastic or gold) curves tend to become normal as the proteins fall to normal. The positive cerebrospinal fluid complement fixation test in a like manner progresses toward normal. The rate at which the complement fixation test becomes normal depends upon two factors: (1) the duration of infection in the patient and (2) the degree of positivity, i.e. the titer of the cerebrospinal fluid before treatment is given. He also found that the overall beneficial effects on the cerebrospinal fluid were approximately 90 per cent regardless of the type of neurosyphilis. There was evidence of cerebrospinal fluid relapse in only 10 per cent of the patients.

Because of the diversity of clinical response and the variation in criteria established by different observers, no statistics on clinical improvement will be presented. The clinical response of neurosyphilis to penicillin has varied from complete relief of symptoms to progression and death in spite of therapy.

EVALUATION OF RESULTS OF SPECIFIC TYPES OF NEUROSYPHILIS. *Asymptomatic.* The evaluation of penicillin therapy in cases of asymptomatic neurosyphilis is based entirely on laboratory findings. Penicillin therapy for asymptomatic neurosyphilis is felt to be effective. Few if any cases under therapy show signs of progression and the cerebrospinal fluid abnormalities return to normal following therapy. The cell count is reduced to a striking degree and usually returns to normal within 10 to 24 weeks. The cerebrospinal fluid proteins generally revert to a normal level in approximately 6 months and remain there. The complement fixation titers

Diffuse Meningovascular Syphilis. Meningovascular neurosyphilis and asymptomatic neurosyphilis respond similarly to penicillin therapy at least from a laboratory standpoint. The clinical improvement in meningovascular syphilis usually is good but will depend upon the amount of permanent damage.

Acute Syphilitic Meningitis. Penicillin therapy for acute syphilitic meningitis has produced excellent results with prompt symptomatic improvement. The symptoms of headache, stiff neck and cranial nerve paralysis quickly disappear and there is gradual improvement of nerve deafness and relief of convulsions. Serologic and cerebrospinal fluid findings revert to and remain normal.

ge
of
tar

paresis or taboparesis. Studies of groups of investigators under the sponsorship of the National Institute of Health show that mental improvement can be expected in about 50 per cent of the patients with paresis but in 20 to 40 per cent there is no improvement or deterioration and in 6 to 10 per cent death occurred within 2 years after treatment. Stokes and his associates showed that the results arising after malaria therapy appeared superior to the penicillin results after the first or second year of observations but were equalled using penicillin therapy after the third year. Improvement in the cerebrospinal fluid abnormalities is superior with penicillin therapy. Many instances of improvement in speech and writing defects, tremor and other neuropsychiatric symptoms are seen.

Tabes Dorsalis. The efficacy of penicillin therapy in tabes dorsalis has been definitely proved. Stokes and his associates indicate that 80 per cent of the patients with tabes dorsalis having Type III spinal fluids (marked increase in cell count and total protein) achieved marked improvement after the third year. The improvement in cerebrospinal fluid abnormalities after the second year is twice as good with penicillin as with malaria therapy. Solomon states that penicillin therapy is highly effective in bringing the cerebrospinal fluid to normal. He feels

fection

Serologic tests respond in a manner similar to those in patients with early or late syphilitic infections not involving the spinal fluid.

that early diagnosis and treatment of patients with tabes dorsalis will produce the best symptomatic results

Taboparesis The studies of Stokes and his associates show that 60 per cent of cases in their series of taboparesis had marked improvement in the cerebrospinal fluid abnormalities at the end of 3 years. They feel that cerebrospinal fluid improvement is superior with penicillin alone and that symptomatic improvement is equal to malaria therapy after the second year.

Syphilitic Epilepsy (Nonparetic) Penicillin

therapy produces no clinical and only moderate cerebrospinal fluid improvement. Few cases of Erb's spinal paraplegia treated with penicillin have been reported.

Nerve Deafness Cranial nerve palsies occurring in early meningeal syphilis usually

impairment in hearing however has been arrested in other patients.

CRITERIA OF TREATMENT FAILURE Treatment failure in neurosyphilis is manifested either by progression of clinical or laboratory findings or as is most common both. It is

progression in spite of normal or improving cerebrospinal fluid findings.

Careful serial study of the cerebrospinal fluid findings either will confirm a clinical treatment failure or predict its potential occurrence.

Using the Dattner-Thomas concept of cerebrospinal fluid activity most of the failures will show an initial increase in cell count and quantity of total protein present. Later the colloidal protein (mastic or gold) test and the complement fixation test will become more positive.

RE-TREATMENT When the initial course of penicillin fails in patients with asymptomatic

neurosyphilis, acute syphilitic meningitis and meningovascular syphilis it is recommended that the total dose of penicillin and the duration of therapy be doubled.

When the degenerative types of neurosyphilis fail to respond to the initial treatment it is recommended that the total penicillin dose and interval of administration be doubled in addition to receiving a full 50 hour course of hyperpyrexia concurrently.

REACTION TO THERAPY Penicillin treatment reactions are found in all stages of neurosyphilis. About 25 per cent of all patients with neurosyphilis treated by penicillin will show a mild febrile Jarisch-Herxheimer reaction. Local Jarisch-Herxheimer reactions characterized by an increase in symptoms frequently are seen. A series of patients with general paresis treated by Callaway and his associates showed increase in symptoms in approximately one third of the cases. Moore believes that therapeutic shock is an all or none phenomenon and therefore advocates administration of full therapeutic doses of penicillin unless specific contraindications exist in the individual case.

and with the same frequency suggested management is the same as that under early syphilis.

Miscellaneous Problems Associated with the Treatment of Syphilis **ORAL PENICILLIN** The oral penicillin treatment of syphilis is mentioned only to be condemned. Oral penicillin preparations although improved still require large doses and prolonged administration for syphilotherapy. This immediately places the control of administration in the patient's hand. Self therapy of syphilis is felt to be too precarious to recommend it for large scale use.

The Effect of Penicillin Therapy for Other Purposes as a Source of Confusion in Management of Syphilis Penicillin is used for innumerable purposes at present so that the unrecognized syphilitic patient may be given varying amounts of penicillin for other diseases before the syphilitic infection is discovered. Such a situation will obviously confuse the evaluation of the patient's syphilitic infection.

Penicillin therapy for gonococcal urethritis and cervicitis is one of the most important sources of such confusion. Various possibilities will be outlined. It is conceivable that the therapeutic penicillin dose used for the gonococcal urethritis could cure completely a coincidental syphilitic infection. On the other hand the incubation period of the primary lesion may be delayed or it may permit an asymptomatic infection to develop. Generally the amount of penicillin for the urethritis should be considered as inadequate for a syphilitic infection and each patient should be followed carefully to eliminate syphilitic relapse manifestations.

It is recommended that all patients with gonococcal urethritis or cervicitis be followed clinically and serologically for 4 to 6 months after their penicillin therapy. The patient should be seen bi-monthly for 2 months and monthly thereafter to have a physical inspection and a serologic test.

When penicillin therapy is started or completed before the positive serologic test is discovered the following procedure is suggested. Immediate arrangements for a complete syphilitic evaluation should be made. This examination should include a careful history, physical examination, quantitative blood serologic test, a cerebrospinal fluid examination and fluoroscopy of the heart and great blood vessels. The accumulated information often will result in clarifying the situation. On the basis of the diagnosis the need for further therapy can be decided. The initially administered penicillin may be adequate or a complete course of penicillin may need to be instituted. Appropriate follow up studies should be made after therapy to insure favorable results.

Caution in making a diagnosis of syphilis is urged since other conditions which respond to penicillin may produce a biologic false positive reaction.

One Day Abortive Therapy for Sexual Contacts of Patients with Early Syphilis
Alexander and Schoch, for several years after the advent of penicillin therapy treated contacts of patients with proved early syphilis with one day abortive antisyphilitic therapy. Their results show that of 130 untreated sexually exposed patients 76 developed clinical syphilis as compared with 115 sexually exposed abortively treated patients of whom

only 6 developed syphilis at a later date. Second contacts with infected persons could not be excluded in the 6 failures. This abortive therapy has potentialities in the prophylaxis against syphilis but further long term follow up studies are required to confirm its effectiveness. This program is still in the investigational stage and its general use is not encouraged.

New Antisyphilitic Agents Recent preliminary reports indicate that aureomycin (*duromycin*) is effective against *Treponema pallidum* infections in man. The material is administered orally and appears to alter the syphilitic infection much as penicillin does. Further investigation will be required before more definite statements can be made about its effectiveness.

Prevention or Control of Syphilis The dream that a rapid method of treating syphilis would eradicate it from society has not been realized with penicillin therapy. Control of syphilis still depends on the epidemiologic follow up on contacts and potential sources of infection as well as treatment. The foundation of such a combination of effort is the private physician or practitioner for to be effective each physician must obtain as much information from each venereally infected patient as possible concerning his source of infection or other possible contacts. From such information he can get the potentially infected patients under his observation or turn the information over to his local health department for further action. The failure to discover and treat infections among contacts leaves an unchecked source of in-

health department is essential if the community and ultimately the country are to control syphilis.

J LAMAR CALLAWAY
ARTHUR H FLOWER Jr.

TROPICAL TREPONEMATOSES (Yaws)

Yaws is an infectious nonvenereal contagious disorder caused by the *Treponema pertenue* which exists endemically in certain tropical countries and occurs primarily in children and adults of the dark skinned races.

Clinically the disease appears in three rather distinct stages. The primary lesions usually are solely cutaneous. The secondary lesions involve the skin and often have associated systemic symptoms. The late or tertiary stage is characterized by gumma formation in the skin and bones. Lymph node involvement is a common occurrence in yaws.

It has long been known that yaws will re-

of syphilis it was suspected that penicillin would be effective against yaws and it was proved by the studies of Dwinelle, Sheldon, Rein, and Sternberg. A dosage of 1,200,000 units of crystalline procaine penicillin G given on an ambulatory basis appears adequate. Two intramuscular injections of 600,000 units each on alternate days are apparently as effective as therapy every 3 hours for 4 days. The repository form of crystalline penicillin G in oil with 2 per cent aluminum monosterate is the most effective recent product. Patients between 6 and 12 years of age are given 600,000 units; those between 13 and 16 years of age are given 900,000 units; a total dose. All patients above 17 years of age are given 1,200,000 units of penicillin.

Evaluation of Results. General observations show that the primary and secondary lesions of yaws respond rapidly and uniformly to penicillin therapy. Most of the lesions disappear within the first week. The late clinical manifestations of yaws improve more slowly.

Serologic response to treatment, however, is quite different. Out of a large group of 466 patients, only 16.6 per cent of the entire group became seronegative at the end of 12 months' observation. If those who showed clinical improvement plus marked diminution in the serologic test are added to the seronegative group, approximately 90 per cent can be considered to have had a satisfactory result. Increasing the total amount of penicillin does not appear to improve the serologic results, although there are some indications that some improvement may be obtained by prolonging the period of treatment. The above conclusions are drawn from patients treated with repository penicillin in beeswax and oil.

Criteria of Treatment Failure. Treatment failure in penicillin therapy for yaws usually will appear as clinical and/or serologic relapse. New lesions may appear and/or the serologic test may show increase in titer if treatment was not effective. Reinfection is an ever-present possibility since the infection is disseminated so widely. The clinical differentiation of relapse from reinfection is sometimes impossible, but for practical management all such cases should be considered as treatment failures.

Re-treatment. Treatment failures should be re-treated by doubling the total penicillin dose and total duration of therapy.

Reaction to Therapy. In the cases studied, no severe reactions were encountered. Approximately one-half of the treated patients showed an elevation of temperature 2 to 8 hours after institution of therapy. Secondary elevations of fever were noted on the third, fourth, and fifth days in approximately one-fifth of the patients treated. These reactions can be considered as systemic Jarisch-Herxheimer reactions.

Allergic reactions following penicillin therapy in yaws were not reported in the series studied.

J LAMAR CALLAWAY
ARTHUR H. FLOWER, JR.

PINTA

This is a nonvenereal disease endemic in the tropical regions of the Western Hemisphere, produced by the *Treponema carateum* and occurs most frequently among the dark-skinned races.

and to

cases
ry re

ports show that 1,200,000 units of repository crystalline procaine penicillin G in oil with 2 per cent aluminum monosterate is effective. Several schedules of administration were used. The method using a single injection technique appeared to give satisfactory results. More prolonged schedules of administration are under study.

The evaluation of the clinical improvement and the serologic response must await further observations.

J LAMAR CALLAWAY
ARTHUR H. FLOWER, JR.

BEJEL

Bejel is a nonvenereal treponemal infection occurring only among Bedouins of the Euphrates Valley. The disease occurs primarily in childhood. The spread of the disease is by personal contact from child to child or child to adult. Certain fomites such as utensils and other objects may be incriminated in the transmission of bejel. Early clinical lesions usually are desquamating grayish nonulcerating patches on the oral mucous membranes. The most common late lesions are ulcerations of the nasopharynx, nodular lesions of periarticular areas, and hyperkeratotic lesions on the soles of the feet. Painful osseous gummatous lesions have been observed. Visceral manifestations of bejel are unknown.

The complement fixation and flocculation tests for syphilis are almost always positive in bejel, particularly in the late stages. Bejel is apparently not passed from mother to fetus in utero.

The lesions of bejel will respond to heavy metal syphilitic therapy. By analogy it is assumed that penicillin will be an effective therapeutic measure. The total dose of penicillin and the formula of administration used for the other tropical treponematoses will probably be effective.

J LAMAR CALLAWAY
ARTHUR H FLOWER JR

REFERENCES

- General Editorial. Present Status of Penicillin in Treatment of Syphilis. Parts I and II. *The Bristol Digest* 5 10 6 1 1948
- Heller J R Jr, Bowman R W and Price E V. Rapid Treatment of Early Syphilis. Progress Report December 1947. *J Ven Dis Inform* 29 103 1948
- Moore J E. Present Status of Penicillin in the Treatment of Early and Late Syphilis. Lecture Post-Graduate Medical Course Los Angeles California April 22 1948
- Moore J E. *Penicillin in Syphilis*. Springfield Ill: C C Thomas 1946
- Moore J E. *The Modern Treatment of Syphilis* with the collaboration of Jarol M Kemp and others. Springfield Ill: C C Thomas 1944
- Stokes J H, Beerman H and Ingraham N R Jr. *Modern Clinical Syphilology: Diagnosis Treatment Case Study*. Philadelphia W B Saunders Co 1944
- Syphilis Study Section. National Institute of Health. Status of Penicillin in Treatment of Syphilis. *JAMA* 136 873 1943
- Etiologic Agent. Cumberland M C and Turner T B. The Rate of Multiplication of *Treponema pallidum* in Normal and Immune Animals in Culture. *Exper Biol & Med* 63 240 1946
- Magnuson H J. Current Concepts of Immunity in Syphilis. *Am J Med* 5 641 1948
- Immunity. Frazier C N and Hung Chung L I. *Racial Variations in Immunity in Syphilis: Study of Disease in Chinese White and Negro Races*. Chicago: University of Chicago Press 1943
- Magnuson H T. Current Concepts of Immunity in Syphilis. *Am J Med* 5 641 1948
- Nelson R A Jr. Factors Affecting the Survival of *Treponema pallidum* in Vitro. *Am J Hygiene* 48 120 1948
- Serologic Test. Neurath H. Biologic False Positive Reactions in Serologic Tests for Syphilis. *Am J Med* 5 670 1948
- Method of Action of Penicillin. Hobby G L, Meyer K and Chaffee E. Observations of Mechanism of Action of Penicillin. *Proc Soc Exper Biol & Med* 50 281 1942
- McDermott W, Benoit M and DuBous R. Time-Dose Relationships of Penicillin Therapy. Regimens Used in Early Syphilis. *Am J Syph Gonorr & Ven Dis* 29 345 1945
- Reactions to Penicillin Therapy. Barksdale E E. Penicillin in Treatment of Syphilis: Results and Complications. *South M J* 39 929 1946
- McElligott G L M. *Venereal Diseases in Penicillin: Its Practical Application*. London: Butterworth & Co Ltd 1946
- Morgenson W J. Toxic Reactions Accompanying Penicillin Therapy. *JAMA* 132 915 1946
- Olansky S. Herxheimer Reactions of Relatively Small Doses of Penicillin. *J Ven Dis Inform* 28 26 1947
- Thomas E W, Landy M and Cooper C. Reactions to Penicillin Therapy for Syphilis. *J Invest Dermatol* 10 77 1948
- Failure vs Reinfection Following Penicillin Therapy in Early Syphilis. In Symposium on Recent Advances in the Study of Venereal Diseases. Washington D C 1948
- Arnold R C et al. Penicillin Therapy in Early Syphilis. *J Invest Dermatol* 9 269 1947
- Mahoney J F, Wright R W and Trautman J A. The Therapeutic Efficacy of Aqueous Penicillin in Early Syphilis. In Symposium on Recent Advances in the Study of Venereal Diseases. Washington D C 1948
- Sternberg T H and Leifer W. Treatment of Early Syphilis with Penicillin. *JAMA* 133 1 1947
- Thomas M W. Penicillin Treatment of Early Syphilis. *Am J Med* 5 657 1948
- Thomas E W. Treatment of Early Syphilis with

- Penicillin III Bellevue Hospital New York State J Med 49 2439 1947
- Late Latent Syphilis Cole H N Penicillin Treatment of Syphilis with Some Remarks in Retrospect of Syphilotherapy over 100 Years Bull New York Acad Med 24 97 1948
- Stokes J H Recent Advances in Syphologic Diagnosis and Treatment Nonspecific Positive Serologic Test and Use of Penicillin Pennsylvania M J 50 718 1947
- Benign Late Gummatous and Visceral Syphilis Tucker H A Penicillin in Benign Late and Visceral Syphilis Am J Med 5 702 1948
- Cardiovascular Syphilis Conference on Therapy Department of Pharmacology and Medicine Cornell University Medical College and the New York Hospital Treatment of Syphilis New York State J Med 46 2651 1946
- De La Chapelle C E Cardiovascular Syphilis New York Medicine 3 17 1947
- Moore J E Cardiovascular Syphilis Summary of Recent Information with Special Reference to Treatment with Penicillin Am J Syph Gonorr & Ven Dis 33 43 1949
- Porter R H Penicillin in Cardiovascular Syphilis Virginia M Monthly 75 357 1948
- Tucker H A and Farmer T W Penicillin in Cardiovascular Syphilis Early Reactions to Administration Arch Int Med 80 232 1947
- Webster B Medical Progress Penicillin in Treatment of Latent and Cardiovascular Syphilis New York Med 3 15 1947
- Syphilis in Pregnancy Aron H C S Barton R L and Bauer T J Prenatal Syphilis Its Prevention by Use of Penicillin in Treatment of Pregnant Women with Early Infectious Syphilis Arch Dermat & Syph 56 349 1947
- Goodwin M S and Farber M S The Necessity for Treatment of Pregnant Syphilitic Women during Every Pregnancy Am J Syph Gonorr & Ven Dis 32 409 1948
- Ingraham N R Jr Prevention and Treatment of Prenatal Syphilis Am J Med 5 693 1948
- Ingraham N R Jr et al Retreatment of the Pregnant Woman for Syphilis following Penicillin Is Additional Therapy Necessary When Effective Treatment Has Been Given Prior to Conception? Am J Obst & Gynec 56 340 1948
- Congenital Syphilis Barker L P Evaluation of Penicillin Treatment in Early Congenital Syphilis J Ped at 32 516 1948
- Nelson A W and Hanchett L J St Louis Data on Congenital Syphilis Digest Proceedings Fifteenth Venereal Disease Control Seminar Pub Health Rep 2 58 1947
- Platou R V et al Early Congenital Syphilis Treatment of 257 Patients with Penicillin IAMA 129 10 1947
- Venereal Diseases Washington D C 1948
- Neurosyphilis Callaway J L et al Use of Penicillin in Treatment of Syphilis of Central Nervous System Report of 100 Patients Am J Syph Gonorr & Ven Dis 30 110 1946
- Dattner H Treatment of Neurosyphilis with Penicillin Alone Am J Syph Gonorr & Ven Dis 32 399 1948
- Kietland H O Leary P A and Underwood L J Treatment of Neurosyphilis with Combination of Malaria and Penicillin Am J Med 5 470 1948
- Solomon H C Current Status of Penicillin Therapy in Neurosyphilis Am J Med 5 712 1948
- Stokes J H Steiger H P and Gammon G D Three Years of Penicillin Alone in Neurosyphilis Am J Syph Gonorr & Ven Dis 32 28 1948
- Miscellaneous Alexander L J and Schoch A G Results of Treatment of Over 100 Contacts of Patients with Early Syphilis with a One Day Abortive Cure in Symposium on Recent Advances in the Study of Venereal Diseases Washington D C 1948
- O Leary P A Kierland R R and Herrell W E Oral Administration of Aureomycin (Duomycin) and Its Effect on Treponema pallidum in Man Proc Staff Meet Mayo Clin 23 574 1948
- Tropical Treponematoses Ormsby O and Montgomery H Diseases of the Skin Philadelphia Lea & Febiger 1948
- Rein C R Personal Communication
- Rein C R et al Penicillin Therapy of Yaws and Serologic Results Arch Dermat & Syph 57 942 1948

AMEBIASIS

Any concept of the therapeutic approach to the treatment of amebiasis involves serious consideration of the incidence of the disease in a temperate zone climate such as the United States fundamental differences in the nature of the disease in the temperate zone as compared with the tropics and the extent of tissue invasion and means of ascertaining the same before any principles of treatment can be outlined It is of historical interest that the Chicago amebiasis epidemic of 1933 was the first instance of the disease having assumed epidemic proportions in a temperate zone area Epidemic amebic dysentery did occur in British troops stationed in Egypt Macedonia and Palestine during World War I but the circumstances were considerably different from those resulting in the widespread infection of a civilian population as occurred in Chicago

Subsequent to the Chicago epidemic Spector studied 10108 patients in the Chicago area between the years 1933 and 1937 Of this group 4478 persons were without complaints Of the total group surveyed 34 per cent were found to be infected Roda

niche and Palmer continued these surveys made at the University of Chicago Clinics and from 1938 to 1941 studied 2691 patients reporting an incidence of 18 per cent. From 1943 to 1946 Palmer and Prescott studied 1132 patients again at the University of Chicago Clinics with a reported incidence of 14 per cent. During the same time interval covered by the last Palmer report Dolkart and Hedges studied 3605 patients at St. Luke's Hospital Chicago. Of this group 1070 patients had gastro intestinal complaints as their presenting symptoms and 35 per cent had stools positive for *E. histolytica*. An overall incidence of 15 per cent was encountered.

Craig and Faust have tribulated the results of surveys made on population samples in different parts of the country. These results indicate an average incidence of amebiasis ranging from 5 to 10 per cent. Some groups of investigators have claimed incidences as high as 25 per cent of the adult population infected with *E. histolytica*.

In studies at the United States Naval Medical Center Michael gave some clue as to the role of returned service personnel from World War II in creating increased spread of amebiasis. It was concluded that intestinal parasites were not introduced in sufficient numbers to contribute to any public health hazard. Of 1000 Naval returnees from endemic amebiasis areas 89 per cent had positive stool identifications for *E. histolytica*. Of 1000 repatriated prisoners of war from similar areas 31 per cent had positive stools for *E. histolytica*.

Because of the difficulties involved in proper identification of *E. histolytica* the different incidences reported throughout the country can be explained by the different criteria used in the various laboratories for making known groups and densities.

much less rigid diagnostic criteria. It is extremely difficult to distinguish between the trophozoite stage of *E. histolytica*, *E. nana* and *E. coli* and unless the organism is recovered from the wall of an abscess or from a mucous membrane lesion we believe that the organisms must be grown in culture before a positive identification can be made.

This opinion was expressed by Dr. C. W. Rees of the National Institute of Health who collaborated with us in the initial setting up of our laboratory and procedures at St. Luke's Hospital.

These aspects of diagnosis are discussed because the dangers inherent in treating an individual for amebiasis on the basis of an incorrect diagnosis are fully as serious as missing the diagnosis by inept laboratory identification. We share with Dr. Rees and others the opinion that *E. histolytica* can at times be a luminal parasite, the so-called carrier state, without producing active tissue invasion. Stopping diagnostic procedures upon the identification of *E. histolytica* in the stools of patients with gastro intestinal symptoms in the carcinoma-bearing age group cannot be countenanced. Negative roentgenographic studies of the gastro intestinal tract and sigmoidoscopic examination must be carried out before amebicidal therapy is initiated.

Some knowledge of the growth characteristics of *E. histolytica* is essential to a knowledge of a means of growth prevention. It is well known that one of the great obstacles in research studies of the organism is that it cannot be grown in pure culture but rather requires the symbiotic activity of other organisms. Rees by careful technique has been able to grow *E. histolytica* with only one contaminating organism for symbiotic activity and consequently it was possible for him to develop for the first time an antigen of sufficient sensitivity to make possible a reasonably accurate complement fixation test as an aid in the diagnosis of amebiasis if tissue invasion is present. More than 20 years ago Hegner reported a series of observations during which he studied the protozoan content of the stools of various animals in the Baltimore Zoo. It was observed that the carnivores had no protozoa in their stools, omnivores had a moderate number and the herbivorous animals had stools loaded with all varieties of protozoa. He suggested at that time that a high protein low carbohydrate diet might be of value in the treatment of amebiasis in humans. Apparently the carrying out of this suggestion has not become a matter of record because no such reports have been encountered. We have studied several patients

particularly some refractory to all forms of amebicidal therapy, and have found that negative stool cultures may be promptly obtained by such a procedure associated with which there was an amelioration of symptoms. It would seem reasonable that the mode of action of a high protein low carbohydrate diet is to alter the bacterial flora of the intestinal tract in such a way as to make further growth of the amebae difficult by virtue of altering the necessary symbiotic activity of other organisms. These observations are in agreement with the changing concepts of bacterial growth, so excellently demonstrated in the work of Dubos and of Waksman, in which there is less concern with the growth rate of an organism in a culture tube than with the growth rate of the organism in its normal environment where the nutritional effect of serum, exudate, and/or the enzyme systems of other bacteria in the environment are at work.

There is good pharmacologic evidence that the action of the various amebicidal drugs in the test tube is not comparable to their action *in vivo*. Perhaps some of the amebicidal activity is due to alteration of the bacterial flora of the digestive tract, making amebic growth impossible, rather than there being a direct effect exerted on the amebae themselves.

Specific Therapy. IODOXYQUINOLINE COMPOUNDS These are mentioned first because they are the least toxic and have the widest range of usefulness.

Diodoquin This is available in 0.2 gm tablets containing 63.9 per cent of iodine. The daily dosage is from 1.8 to 2.0 gm for 20 days. Repeated courses may be employed freely but as with the other amebicidal drugs adequate recheck stool examinations should be carried out. In chronic refractory cases, 0.6 to 1.2 gm of the drug may be given daily for periods of several weeks. There is some justification for the use of this drug as a prophylactic for individuals who are making trips into known endemic amebic dysentery areas. Two individuals in such a situation in Mexico, were maintained by the author on 0.6 gm daily for a period of 2 years without harmful effect. Untoward reactions may occur in iodine-sensitive individuals, despite the fact that relatively little if any iodine absorption is supposed to take

place from the bowel. On occasion constipation or pruritis may occur following the administration of diodoquin or any of the other

because of the insolubility of the iodine.

Vioform This is supplied in 0.25 gm tablets or capsules containing 41 per cent of iodine. The daily dosage is 0.75 gm per day for 7 to 10 days. It has been suggested that courses be repeated if necessary after a 7 day interval of rest. There would seem to be little reason not to employ this drug in larger dosage, especially in view of the lower iodine content. Apparently 0.75 gm per day was the dosage first recommended and custom has decreed its continuance.

Chiniofon Chiniofon (sodium iodoxy quinoline sulfonic acid containing 26 to 28 per cent iodine) was first introduced by Muhlen and Menk in 1921 and was marketed under the proprietary name of "yatren." It is also marketed under the name of "anayodin." The dosage is the same as for vioform, namely, 0.75 gm daily for 7 to 10 day intervals. It is supplied in 0.25 gm tablets. It would appear that the lower iodine content makes chiniofon less desirable than either vioform or diodoquin as a choice in therapy.

ARSENICALS **Carbasone** Carbasone is available in 0.25 gm capsules, dosage recommended is usually 0.50 to 0.75 gm daily for 7 to 10 days. Chemically, carbasone is p-carbamino-phenylarsonic acid and contains 28.85 per cent of arsenic. The toxicity of this drug is much greater than that of vioform or diodoquin and the occurrence of nausea or exacerbations of diarrhea is more commonly encountered than with the iodoxyquinoline derivatives.

Oral Aldersone In 0.25 gm enteric-coated capsules a pentavalent arsenical has been recommended for the treatment of amebiasis by certain Latin American investigators. It is used, as is carbasone, and in the opinion of the authors, the reports do not indicate any special advantage over carbasone.

EMETINE Emetine is one of the two alkaloids (the other being cephaeline) of ipecac, the root of a Brazilian plant. According to Wmdhaus, emetine is probably an isoquinoline derivative. As with the iodoxyquinoline

derivatives, emetine is not especially effective against *E. histolytica* in the test tube (Allan and Dale and Dobell) but is effective in vivo

Emetine Bismuth Iodide This contains about 20 per cent emetine and may be administered orally. It was recommended first by DuMez and has been used chiefly by some of the British workers. It does produce some gastric irritation and on occasion emesis may result. Dosage 0.2 gm daily administered with meals for a period of 4 days.

Chaparro Armargosa An emetine alkaloid derived from a Mexican cactus this may be used as a fluid extract in doses of 1 teaspoonful three times daily for a period of one week. This also may produce gastric irritation and is best given with meals. Practically none of this drug is available in this country and the authors have employed it on only one occasion.

Emetine Hydrochloride Administered intramuscularly this acts as a cumulative protoplasmic poison. It is especially effective in amebiasis when there is evidence of tissue invasion. It is highly toxic, fatalities have been reported as well as numerous reports in which definite evidence of myocardial changes as manifested by electrocardiographic alterations have taken place. These reports suggest that toxic effects begin to be manifest usually after the administration of 240 to 300 mg in a 4 to 5 day period. When used intramuscularly and/or subcutaneously, despite care in selection of the injection site, tissue necrosis and sterile abscess formation may occur. Various procedures have been recommended: injection of 30 mg twice daily, injection of 60 mg once daily, etc. It is the consensus that not more than 600 mg should be administered in a 10 day interval. In view of the cumulative effect of the drug some clinicians have preferred to give more frequent short courses of emetine, stopping for example after 300 mg have been given in a 5 day interval. In patients with concomitant cardiac pathology and in patients in the older age group, electrocardiograms taken before and at intervals during therapy may serve to indicate the occurrence of any toxic effect on the myocardium at the earliest possible moment. If electrocardiographic changes (i.e., depression or inversion of T waves, decreased

amplitude of QRS deflection, changes in conduction time or changes in ST segment deflection) do appear, the drug should be stopped. Matter reported that emetine appeared in the urine within 20 to 40 minutes after injection. It can continue to be detectable in the urine for 5 to 9 weeks after therapy has been completed implying "some kind of stable deposit in the body, perhaps at the site of injection."

ANTIBIOTICS
Bacitracin This may be had in 10,000 unit tablets for oral use. A final recommendation as to daily dosage level cannot as yet be made. Good reports have been made with daily doses ranging between 50,000 and 100,000 units daily. Apparently no toxic effects have been reported after using the drug orally even for long periods of time. In our hands with only a limited series of observations on a few patients 100,000 units daily for a 10 day interval seemed to produce results equivalent to those obtained with some of the iodoxyquinoline derivatives.

Streptomycin Administered orally, streptomycin has the ability to alter the bacterial flora of the gastro intestinal tract. Various combinations of streptomycin have been used by the writers with satisfactory results. The efficacy of these preparations appears to be related to its effect on the bacterial flora of the intestinal tract because in *in vitro* observations amebic growth is not appreciably

Penicillin Penicillin may alter bacterial flora of the gastro intestinal tract whether administered orally or parenterally. The inactivation of penicillin by the penicillinase elaborated by the colon bacillus makes it a poor selection as a therapeutic agent.

have appeared. As with other antibiotics, amebic growth is not inhibited in the test tube. The action in the gastro intestinal tract in terms of altering the established flora thereby creating a growth environment incapable of allowing *E. histolytica* to survive is the probable mode of action. We have used aureomycin in doses of 0.250 gm every 6

hours for periods of 2 weeks in a limited group of patients. It is too early to evaluate any long term results. The absorption from the gastro intestinal tract would appear to make aureomycin one of the three such amebicidal agents (emetine and chloraquin being the other two) worth considering for administration to patients with evidence of tissue invasion.

Chloromycetin. Chloromycetin would appear to have a role in the therapy of amebiasis in terms of its effects on the bacterial

SULFONAMIDES. A few reports have appeared suggesting some usefulness to the employment of the poorly absorbed or non-absorbable sulfonamide preparations such as sulfaguanidine and succinylsulfathiazole. Their mode of action probably is related to the inhibition of amebic growth resulting from alteration of the bacterial flora of the intestinal tract. The dosage varies between 60 and 120 gm a day.

CHLORAQUINE DIPHOSPHATE (7-chloro-4-[4-diethylamino-1-methylbutylamino]quinoline diphosphate). This is one of the newer antimalarial drugs. It is almost completely

absorbed from the lungs. Approximately 10 to 20 per cent of the drug can be recovered in the urine, the remainder being metabolized by the body. Headache of varying severity, pruritis and blurring of vision are some of the toxic manifestations. Manson Bahr reviews cases of amebiasis treated with chloraquine, including a case of amebic hepatitis which was refractory to treatment with other drugs. A

appropriate in the treatment of patients with evidence of tissue invasion.

General Comment

The chief controversy is over the choice of drug. There is no agreement that when one variety of amebicide does not work, then another should be tried. Many of the recommendations obviously are quite arbitrary and represent empirical thoughts on the subject rather than critical evaluation of scientific evidence.

It seems to be the consensus that in the presence of hepatic amebiasis, hepatic abscess, or other sites of extragastro intestinal tract involvement, emetine is the drug of choice. The weight of opinion favors emetine as the preferred drug in the case of early amebiasis with acute dysentery and fulminating symptoms. Most dissonant are the discussions as to the use of emetine in the chronic milder forms of the disease. The writers do not wish to make any dogmatic recommendations. In our use of the drug, however, we reserve emetine for those patients with evidence of an active phase of tissue invasion. The severity of the diarrhea and of the proctoscopic findings, the presence of a positive complement fixation test, and the evidence of extragastro intestinal involvement are some of the criteria that enter into the problem. A large part of the decision is also based on judgment, and unfortunately there is no associated laboratory test which determines its application.

If a decision to use emetine has been made,

the patient should be at bed rest during therapy, especially those individuals in the arteriosclerotic age group, serial electrocardiograms should be taken so that toxic effects on the myocardium can be promptly detected, and therapy discontinued or reduced in intensity if necessary.

Our own opinions as to the choice of amebicides may be summarized as follows:

- (1) If tissue invasion is present as evidenced by the proctoscopic findings, blood and mucus in the stools, extragastro intestinal tract involvement, and a positive complement fixation test, the administration of an amebicidal agent which is not absorbed from the gastro intestinal tract is not

of appreciable value Emetine aureo

(2)

sion any of the lumen acting drugs may be selected

RALPH E. DOLKART
FRED L. DEX

REFERENCES

- Allan W. The Effect of Emetine on *Entamoeba histolytica* in Stools. *J Pharmacol & Exper Therap* 16:21 1920-21
- Craig C. F. and Faust E. C. *Clinical Parasitology* Philadelphia Lea & Febiger 1940
- Dale H. H. and Dobell C. Experiments on the Therapeutics of Amoebic Dysentery. *J Pharmacol & Exper Therap* 10:339 1917
- Dolkart R. E. and Hedges R. N. Present Incidence of Intestinal Infestation with *E. histolytica* and Other Protozoa in Chicago Area. *Gastroenterology* 9:170 1947
- DuMez A. G. Two Compounds of Emetine Which May Be of Service in the Treatment of Entamoebiasis. *Philippine J Sc* 10(B):73 1915
- Hegner R. Carnivorous Diet in Treatment of Flagellate Diarrhea. *JAMA* 83:23 1924
- Manson Bahr P. The Treatment of Amebic Liver Abscess with Chloroquine. *J Trop Med* 57:91 1949
- Mattei C. Toxicité élimination urinaire et accumulation de l'émétine chez l'homme. *Bull et mém Soc méd d'ôp de Paris* 44:531 1970
- Michael P. Intestinal Parasitism. Statistical Study on 1000 Patients Recently Returned from Pacific Area. *Duty U S Nav M Bull* 46:1539 1946
- Palmer W. L. and Prescott A. H. Personal Communication
- Rees C. W. Personal Communication
- Rees C. W. Pathogenesis of Intestinal Amebiasis in Kittens. *Arch Path* 7:1 1929
- Rodaniche E. C. and Palmer W. L. Current Experiences with *E. histolytica* Infection in Chicago. *Illinois M J* 81:458 1942
- Spector H. K. Amebiasis in Chicago. December 1933 to June 1936. *Am J Pub Health* 27:694 1937
- Winhaus A. Cited in Sollmann T. H. *A Manual of Pharmacology* Ed 5 Philadelphia W. B. Saunders Company 1934

FLAGELLATE DYSENTERY

Giardiasis Giardiasis is a clinical entity in the light of present knowledge implies nothing more than the presence of the protozoan *Giardia lamblia* (*Giardia intestinalis*) in the intestine. According to reports it apparently occurs more frequently in children than adults but its identification in the stools

of children or adults cannot be correlated with the occurrence of digestive symptoms. A significant group of patients was reported by Hartman and Kyser at the Mayo Clinic in which digestive symptoms improved after the institution of therapy. These data are difficult to evaluate but in the writers' experiences the conclusion was forced upon them that *Giardia* represent luminal parasites which are nonpathogenic. No treatment is recommended. In view of the equivocal aspects of the clinical significance of this protozoan if for any reason therapy is desired the principles have already been outlined in the discussion of amebiasis. Hartman and Kyser have recommended the use of

amebocidal drugs are not as efficient as in the treatment of amebiasis which might well be due to the fact that the usual habitat of *Giardia lamblia* is the upper small intestine rather than the large bowel as in the case of amebae. The same opportunity for the effect of the amebocidal drugs on the bacterial flora of the large bowel probably does not prevail.

Balantidiasis In contradistinction to the foregoing flagellate *Balantidium coli* is known to produce ulceration and tissue invasion in the colon of man. Manlove, Strong, Walker and Lynch have reported on these occurrences. Walker found that in experimental infection of monkeys with organisms from man and swine *Balantidium coli* had the ability to penetrate normal intestinal mucosa producing ulceration of the submucosa and muscularis. As in amebiasis the cecum is one of the predominant sites of involvement. Acute fulminating symptoms with blood and mucus in the stools may occur or the manifestations may be chronic and low grade in character as in amebiasis. In some instances as in this disease *Balantidium coli* may exist as a luminal parasite with no symptoms or findings attributable to its presence. Specific treatment is somewhat uncertain.

Rectal instillations have been recommended by numerous workers. The instillations have included quinine (1:1000 solution) (Dobell), quinine hydrochloride (0.75 gm in 300 cc water), iodine solution

(1:10 000 solution) silver nitrate (1:3000 solution) It would seem reasonable to assume that if the cecum is the most frequent primary site of invasion rectal instillations would accomplish little toward eradication of the parasite This has been the experience at least as far as amebiasis is concerned and rectal instillation of medication for this disease has largely been abandoned

ORAL THERAPY Oral administration seemingly is more logical both in terms of possibly preventing growth of the organism by

the case of *Giardia lamblia* has dubious significance Many reports have been reviewed by Lynch and the reader is referred to his text for a more detailed discussion The consensus is that this flagellate protozoan is a luminal parasite and its presence does not correlate with the occurrence of symptoms or intestinal lesions

RALPH E. DOLKART
FRED L. DEY

REFERENCES

- Dobell C. Quoted by Lynch
Hartman H. R. and Kyser F. A. *Giardiasis and Its Treatment* JAMA 116:2835 1941
Haughwout F. G. and Domingo E. *Protozoologic and Clinical Studies on the Treatment of Protozoal Dysentery with Benzyl Benzoate* Treatment of Case of Acute Balantidiosis Recovery Death from Other Causes Failure to Find the Parasites in Bowel Lumen and Gut Wall at Autopsy Philippine J Sc 16:633 1920
Lynch K. M. *Protozoan Parasitism of the Alimentary Tract* New York: The Macmillan Company 1930
Minto C. H. Two Cases of Balantidial Colitis Philippine J Sc 12:149 1917
Strong R. P. The Clinical and Pathological Significance of *Balantidium coli* Pub Bur Gov Lab Manila 26:1 1904
Walker E. L. Experimental Balantidiasis Philippine J Sc 8:333 1913

cides seem worth using plus quinine at a brine and as suggested by Haughwout Domingo and deLeon a 20 per cent alcoholic solution of benzyl benzoate given in doses of 30 drops the first day 45 drops the second day and 60 drops the fourth day In their case report the medication was continued for 22 days the patient dying on the 33d day of an allegedly unrelated disease In view of the known highly toxic effects of benzyl benzoate the drug should be used with caution

Trichomoniasis The occurrence of *Trichomonas hominis* in the stools of man as in

DISEASES OF DOUBTFUL ORIGIN

ERYTHEMA NODOSUM

Erythema nodosum is now generally thought to be one of the diffuse collagen diseases that result from hypersensitivity Infections of the upper respiratory passages tuberculosis rheumatic fever coccidioidomycosis and such medicaments as the halides and sulfonamides have been mentioned as etiologic agents It is interesting to note that in European countries the disease is usually thought to be related to tuberculosis whereas in this country more stress is placed on infections of the upper respiratory passages

Treatment of this disease is directed primarily to correcting or removing the etiologic factor or factors involved Infections of the upper respiratory passages should be appropriately treated The presence or absence of tuberculosis or coccidioidomycosis should

be determined The halides sulfonamides and related preparations should be avoided

Bed rest is a most important factor in

to disappear in the recumbent position In general bed rest should be maintained until the patient has been afebrile for at least a week and until the sedimentation rate has fallen to within normal limits and provided no new lesions have formed It is most important to demonstrate the absence of any cardiac involvement because of the frequent association of erythema nodosum and active rheumatic fever

Particular care should be taken to protect the involved extremities The nodules may be extremely painful and in instances even the weight of the bedclothes may be intolerable

erable A heat cradle is usually satisfactory for supporting the bedclothing Heat itself gives a certain measure of relief

Analgesics are indicated when the pain is severe Salicylates are the drugs of choice for the analgesic as well as the antipyretic effect There is some evidence that large doses of salicylate (sodium salicylate, 20 grains q i d, or 12 gm) tend to shorten the course of the disease

There is some indication that the antihistamines may either cure or greatly shorten the course of the disease Pyribenzamine (50 mg t i d) is the drug that has been used most frequently

It should be pointed out that erythema nodosum may remain active for periods of several weeks to months and that frequently patients become discouraged with their apparent lack of progress An awareness of this problem by both physician and patient does much to simplify some of the problems of morale which may otherwise make proper care difficult

RALPH E DOLLART
FRED L DEY

DISSEMINATED LUPUS ERYTHEMATOSUS

Disseminated lupus erythematosus is a generalized systemic disease which occurs in acute, subacute, and chronic forms It occurs in females in 60 to 80 per cent of the cases, usually in the second and third decades of life

Drugs have been utilized with equivocal results It is difficult to evaluate the treatment in a disease which is chronic in nature and subject to remissions and exacerbations

Gold colloid has long been the favorite remedy of dermatologists in the chronic form of this disease The results have been uniformly poor Schmidt, in 1947, treated a series of cases with colloidal gold sulfide in conjunction with vasodilators He theorized that the poor results in previously treated groups were due to vascular spasm at the site of the lesion and failure of the gold to reach the unhealed active lesions Results in his series were gratifying He recommends an initial dose of 2 cc of colloidal gold sulfide, by either the intravenous or intramuscular route This is increased to 3 cc and even 4 cc at intervals of 4 days after which

5 cc should be administered every 5 to 6 days To increase vasodilatation, 100 mg of nicotinic acid are taken after each meal and an additional 100 mg 5 minutes before the injection of the gold compound

Bismuth, by the intramuscular route is also utilized in the treatment of the chronic form of the disease The results again are controversial Sawicky, in 1947, recommended the use of oral bismuth (sodium bismuth trihydrocollanate) His results were not impressive

The heavy metals should be used with caution and should be avoided in the acute forms of the disease because of their tendency further to depress the bone marrow function and increase the severity of the renal damage The treatment of acute disseminated lupus erythematosus at the present time is even more hopeless than the treatment of the chronic varieties Bed rest is essential Exposure to light tends to aggravate the disease Hence the patient should be kept in a darkened room A high vitamin intake is usually recommended, although there is no reason to believe that this favorably alters the course of the disease Because of the tendency of this disease to occur in females during the childbearing years an endocrine factor has long been suspected Large doses of estrogens, androgens and even castration have not altered the course of the disease

Penicillin, streptomycin, and the sulfadiazines have no effect although they are recommended for the treatment of secondary infections Some clinicians recommend the use of these drugs prophylactically to prevent the secondary infections that are prone to occur in this disease

In view of the widespread involvement generally observed in disseminated lupus numerous nonspecific therapeutic measures are in order although the disease process will not be altered Treatment of the cardiac and renal involvement by attention to electrolyte requirements, and administration of oxygen are in order

Some of the recent studies by Rich and his co workers suggest an allergic basis for the disease and classify lupus as one of the diffuse collagen diseases along with periarthritis nodosa, rheumatic fever, and hypersensitive serum and drug reactions The use of anti

histaminic drugs has not favorably influenced the course of the disease up to the present time

The recent use of cortisone (adrenocortical hormone factor E) by Hensch and his co workers and the use of the adrenocorticotrophic hormone of the pituitary (ACTH) may be expected to influence favorably the course of the disease

RALPH E. DOLKART
FRED L. DEY

REFERENCES

- Schmidt F R. Lupus Erythematosus Treated with Vasodilators and Colloidal Gold Sulfide. *Arch Dermat & Syph* 56:248 1947
Sawicky H H. Bismuth (Sodium Bismuth Tritylglycollamate) Administered By Mouth In Treatment of Chronic Discoid Lupus Erythematosus. Preliminary Report. *J Invest Dermat* 9:159 1947

INFECTIOUS PLEURODYNIA

Infectious pleurodynia is a disease which occurs in epidemics and is characterized by fever, headache and severe pain over the area of attachment of the diaphragm. The etiology is unknown but it is thought to be due to a filtrable virus.

There is no specific treatment. The pyrexia and severe chest pain are usually controlled by large doses of salicylates (1 to 15 gm every 4 hours). In severe cases morphine sulfate 15 mg by hypodermic injection may be necessary. The local application of heat gives some measure of relief. A chest binder may be resorted to particularly if an associated cough exaggerates the pain.

The disease is self limited and usually runs its course in 4 to 10 days. One or more recurrences are common.

RALPH E. DOLKART
FRED L. DEY

REITER'S DISEASE

This triad of polyarthritides, urethritis and conjunctivitis is of unknown etiology. The disease is self limited, one or more recurrences are not uncommon.

Penicillin and sulfonamides do not alter the course of the disease; the treatment therefore is chiefly symptomatic.

The joint involvement is usually multiple

and the pain may be severe. Heat and massage give some measure of relief. Salicylates (1 to 15 gm every 4 hours) may also decrease the joint pain. Physical therapy should be started early to prevent deformity.

The eyes should be cleansed frequently with boric acid solution.

Bland urethral irrigations (1:6000 permanganate of potash or 1:10,000 oxymercure cyanide of mercury) and hot sitz baths have been recommended for the genito-urinary infection.

Gold therapy has been suggested in the treatment of this condition. The toxicity of this drug however hardly justifies its use in a self limited disease.

Fever therapy either by an induction cabinet or foreign protein injection may be helpful.

RALPH E. DOLKART
FRED L. DEY

RELAPSING FEBRILE NODULAR NON-SUPPURATIVE PANNICULITIS

(Weber-Christian Disease)

Relapsing febrile nodular panniculitis is a rare disease characterized by recurrent bouts of fever associated with nonsuppurative inflammatory nodules of the subcutaneous tissues.

The treatment is usually symptomatic. No specific therapy is known. Arnold reported on a case which apparently responded to

case which failed to respond to penicillin.

Because of the rarity of the disease and the tendency to remissions, reports of cures in isolated cases should be looked on with suspicion.

RALPH E. DOLKART
FRED L. DEY

REFERENCES

- Arnold H L Jr. Nodular Nonsuppurative Panniculitis (Weber-Christian Disease). Preliminary Report of Case Controlled by Sulfapyridine. *Arch Dermat & Syph* 51:94 1945
Miedemayer A J and Moran J T. Relapsing Febrile Nodular Nonsuppurative Panniculitis. Report of Case Treated with Penicillin. *Ann Int Med* 29:958 1948

TERRAMYCIN*

Terramycin, a new antimicrobial agent produced by the growth of the mold, *Streptomyces rimosus*, is a highly stable insoluble crystalline amphoteric substance which can be reacted chemically with certain acids and bases to form stable water soluble crystalline salts (Finlay et al.) It is effective *in vitro* and *in vivo* against a wide variety of microorganisms, including many of the gram positive and gram negative bacteria both aerobic and anaerobic the rickettsiae and certain of the viruses (Hobby et al., Snyder, Rose). It is especially effective in the treatment of all forms of pneumonia (including primary atypical pneumonia), in acute brucellosis, and in urinary tract infections due to terramycin sensitive organisms as well as in certain other bacterial rickettsial and viral like infections.

Pharmacology **ABSORPTION AND EXCRETION** Terramycin and its salts are substances of relatively low toxicity. Terramycin is absorbed readily following either parenteral or oral administration in animals and man (Hobby et al., Herrell et al., Welch et al., Werner et al.). When the antibiotic is administered by the oral route, more rapid absorption and higher concentrations of terramycin are observed in the serum of patients receiving terramycin hydrochloride than in those receiving the amphoteric form (Hobby et al., Welch et al.). For this reason, terramycin generally is administered orally in the form of terramycin hydrochloride.

The serum content of terramycin is maintained at a fairly constant level for several hours after the oral administration of single 1 gm doses. The concentration begins to decrease about 3 hours after administration of such doses but activity frequently may be demonstrable in the serum for more than 24 hours. Therapeutically effective serum levels of terramycin may be maintained in adults when 1 to 1.25 gm of terramycin are administered orally once every 3 hours. In infants, 33 mg per kilogram of body weight are required to produce concentrations of 0.5 to 1.5 micrograms of terramycin per milliliter

of serum, while single doses of 60 mg per kilogram of body weight produce levels of 1.0 to 4.0 micrograms per milliliter of serum (Hunt et al.).

Terramycin diffuses readily through the placenta and is present in the fetal circulation. When therapeutically effective amounts are present in the blood serum, terramycin diffuses into the pleural fluid. Preliminary observations have suggested that terramycin may not diffuse readily into the cerebrospinal fluid when therapeutically effective blood serum levels are maintained. Hall and his associates, however, have reported one case of an infant with pneumococcal meningitis who responded satisfactorily following

into the cerebrospinal fluid. Hunt et al. have demonstrated furthermore that concentrations of 0.4 microgram of terramycin per milliliter of spinal fluid may be detected in infants receiving single doses of 66 mg of terramycin per kilogram of body weight and showing serum levels of 1.0 microgram per milliliter.

Terramycin appears to be concentrated in the hepatic system and is excreted in the bile. It is excreted in urine and in high concentrations, in the feces in a biologically active form.

TOXICITY Terramycin hydrochloride may be administered orally in large dosages with no signs of toxicity, nonetheless, unlike penicillin, a maximal dosage exists beyond which it cannot be administered parenterally without toxic manifestations. No toxicity has been observed in animals receiving terramycin hydrochloride in dosages of 80 to 500 mg per kilogram of body weight for prolonged periods of time. When administered parenterally, however, some signs of toxicity are apparent in animals when daily dosages of 80 to 100 or 160 mg of sodium terramycin or terramycin hydrochloride per kilogram of body weight are administered intramuscularly over prolonged periods of time (Pan et al., Lepper et al.).

The maximal single dose of terramycin hydrochloride which has been administered to humans is 3.25 gm (49 mg per kilogram of body weight), the maximal daily dose is 15 gm, the maximal total dose, 368 gm. No

* Because of the relatively recent development of terramycin it is hoped that this special section will make a valuable supplement to the preceding chapter on Infectious Diseases.—Editor

untoward reactions, other than nausea, vomiting, and loss of weight after administration for prolonged periods of time, have been observed in a limited number of patients who have received 12 to 15 gm daily by the oral route. It is believed, however, that these dosages represent the maximal quantity that should be used in man.

In patients receiving 1 to 5 gm daily, mild gastro intestinal disturbances have been noted in some instances. The most common reaction is mild looseness of the stools, which in most infectious diseases has a favorable effect. In occasional instances, mild nausea or vomiting may occur, this generally occurs when the drug is administered on an empty stomach and often may be avoided by its administration with cold milk or a light meal. In those patients experiencing nausea

In general, it is believed that 2 gm daily, in divided dosage once every 4 to 8 hours, is adequate for the treatment of most acute infections. Further evaluation may indicate that 1 to 15 gm daily may be sufficient for control of certain mild infections or those due

ADMINISTRATION

It is well known that higher dosages of penicillin on a per kilogram of body weight basis, must be used in infants and children than in adults, if comparable concentrations of antibiotic are to be attained in the blood serum and tissues. This is true of terramycin also. Dosages of approximately 100 to 150 mg of terramycin per kilogram of body weight per day are indicated in the treatment of infections in infants, while adult sized dosages may be used for older children.

Terramycin should be administered by the oral route only. Full dosage should be given

relationship to the size of the daily dose, such reactions are rarely observed with dosages of 1 to 3 gm per day.

There is no evidence that any impairment of renal or liver function occurs when daily oral dosages of 1 to 6 gm are used. Like wise white blood cell and differential counts remain normal during therapy and there is no evidence that terramycin exerts any abnormal effect on the bone marrow. Glossitis, with and without lesions, may occur occasionally. Reactions of an allergic nature, like wise, have been observed in a few instances. Mild allergic reactions and those responding to the usual treatment of such conditions are not contraindications to the further administration of the antibiotic.

Dosage and Administration. Sufficient data are not available to permit a statement of the minimal or optimal dosage required for the treatment of all of the infectious diseases which may respond to the administration of terramycin.

and tissue fluid concentration of terramycin which is adequate to control the infection promptly, and maximal dosage from onset of therapy, therefore, is desirable.

TABLE I

SUMMARY DATA OF 150 TERRAMYCIN TREATED PATIENTS

Diagnosis	No of Patients	Result
Brucellosis	12	Excellent
Typhus	5	Good
Typhoid	4	Doubtful effect
Paratyphoid	2	Doubtful effect
Amebiasis	2	Excellent
Anthrax	1	Excellent
Smallpox	1	No effect
Pneumococcal pneumonia	64	Excellent
Unclassified bacterial pneumonia	20	Good
Urinary tract infections		
<i>Strep fecalis</i>	1	Excellent
<i>E coli</i>	4	Excellent
<i>A aerogenes</i>	2	Excellent
<i>B proteus</i>	8	Poor
<i>Ps aeruginosa</i>	2	Poor
<i>Paracolon bacillus</i>	1	Poor
Erysipelas	4	Excellent
Streptococcal pharyngitis	3	Excellent
Pulmonary tuberculosis	3	No effect
Influenza	4	No effect
Measles	3	No effect
Regional dactis	3	1 Excellent 2 No effect
Ulcerative colitis	1	No effect
Malaria (<i>P vivax</i>)	1	No effect

(From Knight, U. New York State J Med, 1950.)

for at least 48 hours after the temperature becomes normal and acute symptoms have subsided, diminishing dosages are recommended for an additional 48 hours thereafter.

Diseases in Which Terramycin Is Effective **PNEUMONIA** Terramycin may be used satisfactorily in the treatment of essentially all cases of pneumonia. Owing to its

Pneumococcal (Lobar) Pneumonia, with and without Bacteremia Terramycin has been used extensively, by a number of in-

series of 60 patients, whose distribution according to age, sex, and causative type of pneumococcus compared closely to groups which he had treated in previous years with penicillin, observed marked improvement in 59 of the 60 patients with almost complete defervescence within 24 hours after institution of terramycin therapy (5 gm daily). One patient only in this series failed to respond to therapy and died after 4 days of treatment, at necropsy this patient showed evidence of acute rheumatic fever as well as left lobar pneumonia. According to Timpanelli patients with signs of pleural fluid or pleurisy on admission responded readily to terramycin therapy, without requiring drainage. Twenty per cent of these patients were bacteremic at the onset of therapy. There were no cases of pneumococcal meningitis or other purulent complications, following terramycin therapy, within this group of 60 patients. Subsequent studies by Timpanelli and his associates, Tillett et al., and Dowling et al., have indicated that similar satisfactory results may be obtained with lower dosages.

treatment of this infection. In order to minimize the possibility of relapse, it is advisable to continue therapy for periods of 5 to 10 days, depending on the nature and severity of the infection.

Primary Atypical Pneumonia Good therapeutic results have been obtained in the treatment of primary atypical pneumonia

when terramycin has been used in dosages ranging from 2 to 5 gm daily (Melcher et al., Spink, Martin). In general 2 gm daily in divided dosage is adequate, the response is prompt and in most instances the temperature returns to normal within 24 hours.

Friedlander's Pneumonia Little information is available concerning the effect of terramycin in the treatment of pneumonia due to Friedlander's bacillus (*Klebsiella pneumoniae*). The causative organism however, is highly sensitive in vitro to the action of this antibiotic (Hobby et al.). Four recorded cases of proved Friedlander's pneumonia, 2 of these having failed to respond to other forms of antimicrobial therapy, showed defervescence and complete resolution within 5 days after initiation of treatment (4 gm of terramycin daily in divided dosage once every 4 hours for 7 to 10 days).

Mixed Bacterial Pneumonias Terramycin may be used clinically in the treatment of most cases of primary pneumonia due to mixed bacterial floras (*Staphylococcus aureus*, *Streptococcus haemolyticus*, *Streptococcus viridans*, *D. pneumoniae*, *H. influenzae*, *N. catarrhalis*, etc.). In a series of 20 patients, Timpanelli and his associates observed satisfactory responses following administration of this agent. In general however, defervescence occurred more slowly than in patients with pneumococcal pneumonia.

COCCAL INFECTIONS **Streptococcal Infections, with and without Bacteremia** Most strains of hemolytic and nonhemolytic streptococci, including the enterococci (*Streptococcus faecalis*), which are resistant to other antimicrobial agents, are highly susceptible to the antimicrobial action of terramycin. Infections due to hemolytic streptococci, such as septicemia, erysipelas, puerperal sepsis, scarlet fever, acute follicular tonsillitis, septo-

with this antimicrobial agent. Although extensive data are not available to date on the action of terramycin against infections due to nonhemolytic or anaerobic streptococci, one case of a perirectal abscess due to anaerobic streptococci has been reported which showed a prompt response following administration of terramycin in a daily dosage of 2

gm. In another individual with subacute bacterial endocarditis caused by a microaerophilic streptococcus fall in temperature and symptomatic improvement resulted on administration of 4 to 11 gm daily. Prompt symptomatic and bacteriologic responses likewise have been observed in a limited number of patients with chronic pyelonephritis and urinary tract infections due to the enterococci.

Staphylococcal Infections Rantz and his associates have reported that 30 strains of penicillin resistant staphylococci when tested in vitro for their sensitivity to terramycin have shown a remarkable degree of susceptibility to this agent. Infections due to terramycin sensitive strains of *Staphylococcus aureus* including septicemia, endocarditis, cellulitis, acute and chronic sinusitis, bilateral purulent otitis media, furunculosis, impetigo, secondary infections associated with acne vulgaris, conjunctivitis, and urinary tract infections frequently respond rapidly to terramycin therapy (Blake et al.).

Gonococcal Infections Clinical experience indicates that terramycin is highly effective in the treatment of acute gonorrheal urethritis. Hendricks and his associates have demonstrated that two 1 gm doses administered orally at 11 hour intervals are sufficient to cure 100 per cent of patients while two 0.5 gm doses administered at 6 hour intervals are capable of controlling approximately 80 per cent of patients treated. Schoch and his associates on the other hand report that a single 1 gm dose is sufficient to cure essentially all patients with acute gonorrhea. According to these investigators, re-treatment with 0.5 gm once every 6 hours for 3 to 4 doses (i.e. 1.5 to 2.0 gm) is recommended if the response is not prompt.

There is no evidence to date as to whether terramycin is effective in the treatment of chronic gonorrhea or cases with complications such as arthritis, prostatitis, epididymitis or salpingitis; it seems likely, however, that it should be effective.

Meningococcal Infections Little information concerning the effect of terramycin in the treatment of meningococcal infections is available. Preliminary evidence suggests that in some instances terramycin may be adequate for control of meningococcal meningitis. Further studies are necessary to

evaluate its true effect in the treatment of this disease. Meanwhile sulfadiazine remains the drug of choice. However, in severe or overwhelming infections, terramycin or penicillin or both antibiotics should be given in addition.

BACILLARY INFECTIONS *Brucellosis (Undulant Fever)* In vitro studies by Spink and his associates and by Heilman et al. have indicated that terramycin is highly effective against *Brucella abortus*, *Brucella suis*, and *Brucella melitensis* and is capable of exerting a marked suppressive effect on the course of experimental brucellosis in mice. Clinical experience with terramycin indicates that this antibiotic is also highly effective in the

therapy of illness within a few hours after initiation of terramycin therapy in 11 of 12 proved cases. Nine of these were bacteremic (*Brucella melitensis*) while the remainder showed significant elevations of antibody titer. Nine of these patients were febrile on the first day of therapy; in these, defervescence was rapid (average 1.9 days). All patients were ambulatory within one week after beginning therapy, although many of them had been severely ill for more than one month. Bacteremia disappeared at the time of defervescence in some patients but persisted for 3 to 6 days in others. The one individual patient who failed to show a definite response during therapy was a patient in whom extensive bony involvement was present. The dosage used throughout this series was 100 to 150 mg per kilogram of body weight per day until the patient was afebrile, then 50 mg per kilogram per day for a total of 28 days of therapy. None of these patients relapsed during follow-up periods ranging from 2 to 8 weeks.

In a subsequent series of 4 patients, Marones observed an initial good response on administration of similar doses of terramycin for 5 to 7 days only. In all instances, however, relapses occurred following discontinuation of therapy. Prolonged therapy, therefore, is essential in order to minimize the possibility of relapse.

No data are available on the effect of terramycin in the treatment of chronic brucellosis.

Infections Due to Terramycin sensitive

treatment of acute infections such as septicaemia multiple liver abscesses diffuse bronchopneumonia etc. due to *E. coli* *A. aerogenes* and other terramycin sensitive gram negative organisms. It is particularly effective in the control of certain urinary tract infections. Ball and Douglas have reported that a dosage of 250 mg administered orally once every 6 hours for 5 days followed by 125 mg once every 6 hours for an additional 5 days is sufficient to produce a prompt and effective response provided the invading organisms are susceptible and no organic or obstructive disease exists.

King and his associates report similar beneficial results in the treatment of pyelonephritis and postprostatectomy urinary tract infections on administration of 500 mg once every 6 hours for 5 days. According to these investigators this regimen is adequate for the treatment of infections due to *A. aerogenes*, *E. coli*, the enterococci *Ps. pyocyaneus* and *Staphylococcus aureus*. Although *Proteus vulgaris* an organism frequently present in urinary tract infections generally cannot be eliminated some improvement often results when terramycin is administered to patients with mixed infections involving this organism.

Hemophilus Infections Experimental studies in vitro and in animals indicate that *H. influenzae* and *H. pertussis* are highly sensitive to the action of terramycin. In a

24 to 72 hours after initiation of therapy (500 mg once every 6 hours) (King et al.)

Miscellaneous Infections Preliminary evidence suggests that terramycin may be used with satisfactory therapeutic results in the treatment of anthrax and other gram positive bacillary infections, tularemia and bacterial bacteremia.

SPIROCHETAL INFECTIONS Syphilis. Sufficient data are not available to indicate the true value of terramycin in the treatment of syphilis. According to Hendricks et al. clinical healing of syphilitic lesions (primary and early secondary syphilis) occurs promptly

when dosages of 60 mg per kilogram of body weight per day are used for a period of 8 days. In essentially all instances the dark field is reversed within 24 to 48 hours. Two patients who were serologically positive (Eagle precipitation test) at the onset of therapy showed negative serologic results after one month.

RICKET

Experimental studies by Snyder and Smadel indicate that terramycin is a highly effective antirickettsial agent against *R. tsutsugamushi* (scrub typhus) and *R. prowazekii* (epidemic typhus). Knight and his associates have reported 5 patients with typhus (2 murine, 3 epidemic) who were treated with terramycin in dosages of 100 mg per kilogram per day. With the exception of one patient whose temperature reached normal only after slightly more than 96 hours, all were afebrile and convalescent within less than 54 hours after initiation of therapy. Marones has reported a similar response in 5 additional patients within 48 hours after initiation of therapy. A single patient with scrub typhus showed a striking response following administration of a single 8 gm dose (Smadel).

Rickettsialpox Laboratory and clinical studies by Rose and his associates indicate that terramycin is highly active against *R. akari*, the etiologic agent of rickettsialpox. A therapeutic response may be observed within 24 to 48 hours following the administration of daily dosages of 2 to 5 gm.

VIRAL LIKE INFECTIONS **Granuloma Inguinale** A limited series of patients with granuloma inguinale has been treated with terramycin in dosages ranging from 1.5 to 4 gm per day. According to Hendricks et al. degeneration of the Donovan bodies and clinical healing of granuloma inguinale lesions occur promptly when dosages of 60 mg per kilogram of body weight are used daily for periods of 10 days.

Lymphogranuloma Venereum Although the data available are limited, preliminary evidence suggests that terramycin is effective in the treatment of lymphogranuloma venereum.

Miscellaneous Viral like Infections Although it has not been possible to demonstrate that terramycin exerts a specific antiviral action against the virus of herpes zoster, preliminary observations indicate that

may be of value in the treatment of some cases of herpes zoster. Preliminary evidence suggests also that terramycin is of value in the treatment of infectious mononucleosis.

Experimental studies indicate that in high concentrations terramycin is capable of inhibiting the infection of the chick embryo with the PR8 strain of influenza A virus. It has not been possible to demonstrate this effect in experimentally infected mice. Nonetheless, administration of terramycin to patients with influenza in most instances causes rapid reduction in fever and symptomatic improvement (Finland).

PROTOZOAN INFECTIONS *Amebiasis* Terramycin has been used effectively in the treatment of over 235 patients with amebiasis. According to Most and Van Assendelft,

complete disappearance of *E. histolytica* from the stools of all but 1 of 16 carefully controlled patients. Parasitic relapses occurred in the 16th patient on the 11th day after discontinuation of treatment. In the remaining 15 patients an average of 4.2 stools per patient remained negative during observation for an average of 19.4 days of therapy.

MISCELLANEOUS INFECTIONS *Upper Respiratory Infections* Terramycin is excreted in high concentration in the sputum and appears to exert a marked effect on the nature and consistency of the sputum as well as on its bacterial content. In cases of acute bronchitis, pharyngitis, laryngotracheitis, tracheobronchitis, sinusitis, and otitis media, and in chronic bronchiectasis and whooping cough, administration of terramycin often results in prompt symptomatic improvement. Upper respiratory infections, with cough, fever, and hoarseness frequently respond promptly to terramycin therapy. Although there is probably no specific action of the antibiotic on the influenza virus in human subjects, marked symptomatic improvement occurs in patients with influenza within 24 to 48 hours after initiation of terramycin therapy.

Reduction of Fecal Flora Preoperatively and Postoperatively Terramycin is active against gram positive and gram negative micro-organisms, both aerobic and anaero-

bic, and against the enterococci. It is extremely effective, therefore, in reducing the bacterial flora of the feces and may be used advantageously for this purpose preoperatively and postoperatively (Rantz, Pulaski).

Peritonitis The broad antimicrobial spectrum of terramycin makes it exceptionally useful as a chemotherapeutic agent for the control of peritonitis due to mixed bacterial floras (Yeager).

Achlorhydria Striking symptomatic improvement frequently occurs following administration of terramycin in older debilitated patients with achlorhydria who show constant gastro intestinal symptoms (i.e., gas distention, and constipation) due to bacterial growth ascending into the small gut.

Diseases in Which Terramycin Is of Doubtful Value Terramycin has been used extensively in the treatment of typhoid fever and other *Salmonella* infections. In patients with typhoid fever, there has been no evidence of a drug induced response (Knight). In patients with other types of *Salmonella* infection, more satisfactory therapeutic results may be obtained (King et al., Knight).

Experimental studies in vitro and in vivo indicate that most strains of *Ps. pyocyaneus* are highly resistant to the action of terramycin. Occasional patients with such infection have responded to therapy, however, and the role of terramycin in the control of infection due to this organism remains to be evaluated.

No clinical data are available concerning the action of terramycin in the treatment of Rocky Mountain spotted fever or Q fever. Laboratory studies on this group of organisms suggest, however, that terramycin should be effective in their control (Yeager et al.).

Diseases in Which Terramycin Is Ineffective Terramycin is ineffective in the treatment of measles, mumps, malaria, trichinosis, arthritis, chickenpox, and variola. Although experimental studies indicate that terramycin may possess tuberculostatic activity, there is no evidence to date that it is effective in the treatment of tuberculosis in man. The use of terramycin in the treatment of these infections is not indicated.

REFERENCES

- Ball T L and Douglas R G Terramycin in Urinary Tract Infections Presented at San Francisco Obstetrical and Gynecological Society May 1950
- Blake F G et al Clinical Observations on Terramycin *Yale J Biol & Med* (In press 1950)
- Dowling H et al Unpublished Data
- Finland M Unpublished Data
- Finlay A C et al Terramycin A New Antibiotic *Science* 111 2874 1950
- Hall H E Unpublished Data
- Heilman F Unpublished Data
- Hendricks F D et al Terramycin in the Treatment of Venereal Disease *JAMA* 143 4 1950
- Herrell W et al Terramycin Some Pharmacologic and Clinical Observations *Proc Staff Meet Mayo Clin* 25 183 1950
- Hobby G L et al The Absorption and Excretion of Terramycin in Animals *Proc Soc Exper Biol & Med* 73 511 1950
- Hobby G L et al The Antimicrobial Action of Terramycin in Vitro and in Vivo *Proc Soc Exper Biol & Med* 73 503 1950
- Hunt A et al Unpublished Data
- King E Q et al Clinical Observations on the Use of Terramycin Hydrochloride *JAMA* 143 1 1950
- Knight V Clinical Evaluation of Aureomycin and Chloramphenicol Presented at Section on Medicine New York State Medical Society New York *State J Med* (In press 1950)
- Lepper M H et al Studies of Hepatic Intolerance to Large Doses of Aureomycin and Terramycin Administered Parenterally *JAMA* (In press 1950)
- Marones S Unpublished Data
- Martin S Unpublished Data
- Melcher G W et al Terramycin in the Treatment of Pneumococcus and Primary Atypical Pneumonia (In press 1950)
- Most H and Van Assendelft F Terramycin Therapy of Amebiasis *Science* (In press 1950)
- Pan S Y et al The Pharmacology of Terramycin *J Pharmacol & Exper Therap* (In press, 1950)
- Pulaski E J Unpublished Data
- Rantz L Unpublished Data
- Rose H M Unpublished Data
- Schoch A Unpublished Data
- Smadel J Unpublished Data
- Snyder J C The Antirickettsial Properties of Terramycin *Ann New York Acad Sc* (In press 1950)
- Spink W Unpublished Data
- Tillett W et al Unpublished Data
- Timpanelli A See Knight V
- Timpanelli A et al Unpublished Data
- Welch H et al Comparative Studies on Terramycin and Aureomycin Antibacterial Spectrum, Serum Concentrations and Urinary Excretion *J Am Pharm A (Sci Ed)* 39 185 1950
- Werner C et al The Absorption and Excretion of Terramycin in Humans Comparison with Aureomycin and Chloramphenicol *Proc Soc Exper Biol & Med* (In press 1950)
- Woodward T et al Unpublished Data
- Yeager G et al Unpublished Data

CHAPTER II

PARASITIC DISEASES

FLUKE INFECTIONS OTHER THAN SCHISTOSOMIASIS

The flukes are a group of worms, leaf-shaped, varying in size from 1 to 75 mm in length

From the standpoint of therapy, flukes in man can be divided into two groups, those found in the intestinal lumen, and those occurring in tissues and, therefore, more resistant to the action of the usual anthelmintic drugs. It is natural that vermifuges have been used in the treatment of intestinal flukes, usually with considerable effectiveness. For example, *Fasciolopsis buski* infections may be treated by giving two doses of 0.2 gm of beta naphthol or by carbon tetrachloride administered as for hookworm infections. Treatment of infections with *Heterophyes* and *Metagonimus* tetrachloroethylene, as described in this book under Hookworm Disease is recommended.

In infections with somatic parasites the

protozoan somatic infections are emetine, antimonials, and gentian violet these drugs are given parenterally.

Paragonimus infections are acquired by eating raw crayfish or certain fresh water clams. Although the parasite occurs in the United States, human cases are not encountered here because of our dietary habits. The disease is a serious one in that the flukes invade the lungs, producing a clinical picture much like that of pulmonary tuberculosis. The disease is readily distinguished from other pulmonary infections however, by the presence of the characteristic eggs in the sputum. Specific treatment is generally unsatisfactory, although success has been reported with the use of sodium antimonyl tartrate, and Yokogawa et al reported cures in some cases treated with prontosil and

emetine. The symptoms of the disease generally subside in 5 or 6 years after the infection has been acquired and removal from exposure has been beneficial.

Fasciola infections are acquired by eating aquatic plants with encysted larvae. Human cases occur from this source in many parts

namely the adults are found in the bile passages. Treatment is not satisfactory, oleoresin of the male fern (*Aspidium*) as used for tape worm infestation or 1 per cent Magdala rose dye given intravenously has been recommended, emetine and carbon tetrachloride may be beneficial.

Opisthorchis and *Clonorchis* infections are acquired by eating raw infected fish. Adult worms are found in the bile passages. Sodium antimonyl tartrate given intravenously and oral gentian violet in enteric coated tablets may be of value.

Prevention. These flukes occur in the Orient in parts of Africa and a few cases have been reported from Europe. They are all acquired by eating fresh water aquatic plants or fresh water fish, crayfish, or clams. The native food habits determine to a great extent the frequency of occurrence of these infections in man. In many places, these foods are eaten raw or with inadequate pickling to kill the encysted parasites. Americans traveling in these areas should be cautioned not to eat uncooked exotic foods whether served raw or spiced.

FREDERICK J. BRADY

SCHISTOSOMIASIS

Schistosomiasis has become important in the continental United States within recent years because of the acquisition of the disease by members of the armed forces and because of its importation by foreign visitors

The organisms do not multiply within the body and the degree of illness is conditioned by the number of parasites acquired. In severe cases the disease is incapacitating and may cause death. Schistosomiasis is a major cause of illness in Puerto Rico.

Schistosomiasis is acquired from bathing or wading in fresh water containing the cercariae or by ingesting cercariae with drinking water. These cercariae are released from infected snails in enormous numbers, they are free swimming and attracted to man's skin on contact with water. The cercariae penetrate the intact skin of the victim and after about 6 weeks they mature to become an adult worm in the venules of the liver, intestine, or bladder, depending on the species of schistosome. Females in those locations deposit spined eggs in the wall of the venule whence they are carried passively to the lumen of the bile ducts, intestine, or bladder. The clinical disease is produced by the accumulative scarring due to the presence of and passage through tissues of the ova. The ova may secrete a lytic substance that adds to the mechanical trauma.

Chemotherapy cannot be expected to be of value in alleviating the symptoms produced by the tissue injury already present. Chemotherapy should therefore be directed at killing the adult parasites so that more eggs will not be produced, and at killing the ova already in the tissues that may be secret-

antimonyl tartrate and is generally preferred in this country. Neither compound should be sterilized by heating. The compounds are administered intravenously as aqueous or saline solutions up to 1 per cent in strength. Because these salts are caustic to tissues, concentrations of 0.5 to 1 per cent are preferred and less injury occurs in case of extravasation. The injections should be given over an interval of several minutes to avoid the immediate side reactions presumably due to the high blood levels which are produced with the faster administration.

One per cent solutions of tartar emetic in 5 ml ampules are available from the Abbott Laboratories. Solutions may be made up in sterile 5 per cent glucose in saline in physiologic saline, or in distilled water by weighing and adding tartar emetic from a freshly opened bottle of tartar emetic using sterile glassware. Such solutions should be made up fresh each day.

Various schedules of treatment have been used successfully, most regimens require three administrations weekly or, better, an administration every second day. The following schedule is commonly used for adults of average weight. The solution is given every second day for a total of 15 doses if 0.5 per cent solution is used. 4 cc are given the first day and the amount increased at each injection by 4 cc to the largest amount of 28 cc by the sixth injection. The total course contains 14 gm of antimony.

Within the past few years Alves and Blair have successfully used a rapid method of therapy for schistosomiasis. They gave 0.6 to 0.91 gm of sodium antimonyl tartrate in six doses distributed over a 36 hour interval. These authors stressed the necessity of giving the injections slowly.

Stibophen as a 63 per cent aqueous solution is given intramuscularly every second day excepting for the first three doses which are given daily. For an adult the doses are successively 15 cc, 35 cc, and 50 cc until a total of 75 cc has been given.

Mills reported good results with the use of 4 cc of lithium antimonyl thiomalate (each ml containing 10 mg of antimony) given intramuscularly 6 days weekly for 2 weeks. Mills also used 5 cc of stibophen given by a similar schedule with good results.

rhosis which is commonly present and treatment of granulomatous or neoplastic tissues which are often found in the bladder or rectum.

The chemotherapeutic agents of choice have been among the trivalent antimony compounds. The antimonyl tartrates are most widely used because of their cheapness and effectiveness. Less toxic and less irritating to the tissues are stibophen (fudium, manufactured by the Winthrop Chemical Company) and lithium antimonyl thiomalate (anthiomaline, manufactured by Merck and Company). The antimony tartrates must be given intravenously, stibophen and anthiomaline are given intramuscularly.

Potassium antimonyl tartrate (tartar emetic) is more economical than sodium

Side effects of these compounds are similar to those of the trivalent antimony compounds, mentioned above, but differ in degree, the antimony tartrates being more prone to provoke reactions than stibophen or lithium antimony thiomalate. Immediate reactions are likely to be cough, nausea and vomiting, and, rarely, collapse, these reactions are much less likely to occur if the injections are made slowly. During the course of therapy, vomiting, anorexia, diarrhea, weakness, excessive perspiration, loss of weight, and pain in the joints may occur. Tarr, and Schroeder et al. have found that electrocardiographic changes may occur without associated clinical findings referable to the heart or evidence of organic lesions. The untoward symptoms clear up shortly after treatment, the electrocardiograms may become normal in a few days to 2 months.

Caution must be exercised when treating patients with liver and kidney damage. The liver, because of its uptake of antimony, is the organ most affected in antimony intoxication. In chronic schistosomiasis, hepatitis, or cirrhosis must be presumed to be present but the treatment should be administered, except in hopeless cases, to keep further

not be administered concurrently with other metallic compounds or cardiovascular depressants.

FREDERICK J. BRADY

SWIMMER'S ITCH

This disease occurs in the north central states and is due to *Schistosoma cercariae* penetrating the skin but, because man is an accidental host, the schistosomes do not develop to maturity. The cercariae probably die within the skin and release allergens, giving rise to severe itching. Preliminary work by Olivier indicates that antihistaminic agents have value in relieving the distressing pruritus. No individual prophylactic measures have been developed although procedures may be used about bathing areas to reduce the snail population.

FREDERICK J. BRADY

REFERENCES

- Alves W. Intensive Treatment of Schistosomiasis with Antimony. *South African M J*, 19 171, 1945.
- Alves, W., and Blair, D. M. Schistosomiasis, Intensive Treatment with Antimony. *Lancet*, 19 1946.
- Anonymous. Schistosomiasis Japonica. *War Department Technical Bulletin, Med* 167, Washington, D. C., 1945.
- Barter, F. C. et al. Fate of Radioactive Tartar Emetic Administered to Human Subjects. Blood Concentration and Excretion Following Single and Multiple Intravenous Injections. *Am J Trop Med*, 27 403, 1947.
- Mills, W. G. Treatment of Schistosomiasis. *Lancet* 1 12 1946.
- Olivier L. Personal Communication.
- Schroeder E. F., Rose F. A., and Most, H. Effect of Antimony on Electrocardiogram. *Am J M Sc*, 212 697 1946.
- Tarr, L. Effect of Antimony Compounds, Guadin and Tartar Emetic, on Electrocardiogram, Preliminary Report. *Bull U S Army M Dept*, 5 336 1946.
- Yokogawa S. et al. Studies on Treatment of Paragonimiasis. On the Efficacy of Prontosil in Combination with Emetine against Lung Fluke Disease and Changes in the Eggs of Lung Flukes During the Treatment. *Acta Japonica Tropicalis*, 2 23 1940.

TAPEWORM INFECTIONS

With few exceptions, tapeworms require two hosts to complete their life cycles. As larvae, they are somatic parasites encysting in almost all tissues of the host, as adults, they live in the lumen of the intestine. Tapeworms while in the intestine are relatively innocuous parasites and oral treatment is fairly effective. The tissue invading tapeworm larvae that infect man, however, cause serious and often fatal illnesses and no known chemotherapeutic measure is effective against these parasites.

The large adult tapeworm parasites infecting man in the United States are the beef tapeworm (*Taenia saginata*) and the fish tapeworm (*Diphyllobothrium latum*). Less frequently diagnosed but actually more common is the dwarf tapeworm (*Hymenolepis nana*). A common tapeworm of dogs and cats (*Dipylidium caninum*) is sometimes found in children. The pork tapeworm

(*Taenia solium*) is rare in man in the United States. The pork tapeworm and the hydatid tapeworm (*Echinococcus granulosus*) will be discussed under the heading Larval Tapeworm Infections because of the pathogenicity of the larvae in man.

Intestinal Tapeworm Infections. The therapeutic regimen should be designed to clean the intestinal tract so that the worm will be better exposed to a high concentration of the drug. None of the recommended drugs available will always be effective in removing the head of the tapeworm, although all will usually bring away long chains of segments of the parasite. The head of the tapeworm is small and is often difficult to recover in the material passed following treatment, but if it is not found, re-treatment should await the reappearance of segments or eggs in the stools. It is recommended that the stools be examined for segments or eggs about 3 months after treatment, if the examination shows no evidence of the tapeworm the treatment may be considered successful.

The depth that the tapeworm head is buried in the mucosa probably varies from time to time. There is an element of chance, therefore, whether cure will result from treatment. Lack of success is not necessarily due to ineffectiveness of the therapeutic regimen or impotency of the drug but it may be due to the relative inaccessibility of the head to the therapeutic agent.

It is wise to use saline purges and a non-fatty vehicle to lessen absorption of any fat-soluble component of the drug. The safety of the tapeworm anthelmintics lies only in their lack of absorption through the intestinal wall. They produce less nausea and are more effective if given by a duodenal tube.

Tapeworm segments are motile and it has been observed that they contract and may break apart when they strike a cold surface. Better results of treatment have been observed when passages are made into warm water.

The patient should be hospitalized on the day before treatment. Only a light, low residue meal is given in the evening. Thirty to 60 gm of magnesium sulfate, with adequate water, and an enema are given at bedtime.

Breakfast is withheld on the day of treatment and another enema is given. A tube is

passed into the duodenum and its location is checked fluoroscopically. The drug is then given in the prescribed manner. Food is withheld until the bowels move copiously. All movements are passed into a bedpan containing warm water.

CHEMOTHERAPY. The drug most commonly used is oleoresin of aspidium or male fern. This drug deteriorates upon aging and should not be stored over long periods of time. The adult dose should not exceed 6 cc. of the oleoresin and it is best given in divided doses.

Oleoresin of aspidium	6 cc
Powdered acacia	8 gm
Distilled water q s	60 cc

One half of this emulsion is given by a duodenal tube and the remainder is given one hour later with a saline cathartic. Magnesium sulfate may be added to the emulsion. Proportionately smaller doses are used for small adults and children. Pregnancy and diseases of the heart, liver, and kidneys are contraindications to the use of male fern.

Untoward symptoms are vomiting or those of the nervous system indicating absorption, such as headache, vertigo, twitchings, and visual disturbances. The advent of alarming symptoms calls for supportive treatment such as heat, parenteral fluids, and procedures to hasten evacuation.

Carbon tetrachloride and tetrachloroethylene in dosages as for hookworm infections have also been used with success against intestinal tapeworms. Tetrachloroethylene does not cause liver damage in therapeutic doses, but it is less effective against tapeworms than carbon tetrachloride. Hexylresorcinol in doses as for *Ascaris* infections has been used with success against intestinal tapeworms.

Recently several investigators have indicated that atabrine is effective against

3 tablets one hour later and a purge 3 hours later. Of 30 patients treated in this manner, 25 were freed of their tapeworms (*T. saginata*, *T. solium*, and *D. latum*). Several patients had reactions. Some had intense vomiting.

I had discoloration of the skin, and I had abdominal pain

PREVENTION OF INTESTINAL TAPEWORM INFECTIONS The beef tapeworm is acquired by the ingestion of the larvae in undercooked beef and the fish tapeworm is similarly acquired from certain fresh water fish. Beef carcasses are carefully examined for tapeworm larvae at packing plants having trained inspectors, and if larvae are found, the meat is made safe for consumption before being sold. However, locally butchered meat or meats from plants without adequately trained inspectors may harbor the viable larvae. Meat that is shipped across state lines is federally inspected and safe from tapeworms. The fish tapeworm is often acquired from eating gefüllte fish, a Jewish dish containing raw fish. Frequently it is acquired by housewives who taste fish foods during their preparation.

The dog tapeworm is acquired by children

son to person by fecal contamination of the hands, although it is possible that a tapeworm of mice and rats is identical and the disease may be acquired from their droppings.

Larval Tapeworm Infections Generally a tapeworm uses a different host for the larval and adult stages. The pork tapeworm, however, may develop as either a larva or adult in man. A person harboring an adult pork tapeworm is endangered in that reverse peristalsis may carry the eggs from the lower intestine to the high intestine where they will hatch. The embryos can penetrate the mucosa and reach the blood stream to be disseminated throughout the body. In the tissues they grow to larvae about 0.5 cm in diameter, they may occur by the thousands. In the brain these cysticerci manifest their presence in a variety of symptoms such as epileptiform seizures and often cause death when vital areas are involved. The presence of an adult pork tapeworm in the intestine carries considerable significance and treatment should not be delayed. The treatment for the adult tapeworm is the same as for the beef tapeworm. There is no specific treatment for the cysticercosis caused by the disseminated larval forms.

Prevention of the infection is in avoidance of undercooked pork. *Taenia solium* is a common parasite in many of the tropical and subtropical countries and particular care should be taken by travelers to these countries to eat only well cooked pork.

The other larval tapeworm of man is a

the disease is often seen in immigrants. A single egg of this species when swallowed will give rise to a hydatid cyst within which new infected forms develop as the cyst

mucous cyst fluid is allowed to get on other tissues, and if the germinal layer is not completely removed or devitalized. The disease in dogs is acquired from their ingestion of carcasses of infected sheep, cattle, and hogs. Prevention lies in the proper disposal of such carcasses so that dogs cannot become infected from these sources.

FREDERICK J. BRADY

REFERENCES

- Magath, T. B., and Brown, P. W. Standardized Method of Treating Tapeworm Infestations in Man to Recover Head. *JAMA* 83:1543, 1927.
Neghme, R. A., and Farguenbaum, J. Nueva modalidad de tratamiento en las teniasis. *Rev. méd. de Chile*, 75:54, 1917.

ASCARIASIS

In the United States infections with *Ascaris lumbricoides*, the large roundworm, are generally due to only a few worms but occasionally cases are encountered with massive infections. Not infrequently, the first knowledge of the infection is obtained when a worm migrates from the rectum or is vomited. The finding of eggs of *Ascaris* in the feces indicates the presence of at least one female worm but male worms or immature females may be present without being demonstrated by stool examination.

Persons with *Ascaris* eggs in the feces should be treated. In some cases, however, after passage of a single worm the stool examinations reveal no eggs. Empirical treat-

ment is not recommended in these cases but the feces should be examined over a period of several months because of the possibility of immature worms being present when the first worm was passed

Occasionally in the United States and frequently in some other parts of the world patients will be found to harbor hundreds of ascarides. It is in these cases that care must be exercised in selecting an anthelmintic that will rapidly paralyze or kill the ascarides rather than stimulate them because intestinal obstruction may result in the latter case (see Hookworm Therapy)

Chemotherapy The drug of choice for the treatment of ascariasis is hexylresorcinol. The drug is available in gelatin-covered pills (caprokol pills Sharp and Dohme) containing 0.2 gm of hexylresorcinol. A light meal is given on the evening preceding treatment; breakfast is omitted and the full dose is given at one time. The adult dose is 5 pills (1.0 gm of hexylresorcinol) with proportionately lesser doses for children to a minimum of 2 pills (0.4 gm) for children under 6 years of age. Brown recommends 0.1 gm for each year of age up to 10 years. Following the administration of the drug food is withheld for 4 to 5 hours. A saline cathartic is given at 4 to 24 hours after therapy in order to expel the worms. Patients can ordinarily remain ambulant during treatment.

Hexylresorcinol pills should be swallowed without rupturing the coating; otherwise burns of the oral mucosa will result. The use of alcoholic beverages during therapy is contraindicated because hexylresorcinol is especially soluble in alcohol; other fluids may be given freely. Gastroenteritis and peptic ulcer are usually considered contraindications to therapy with hexylresorcinol.

Orally administered hexylresorcinol has little toxicity. Eunhorn, Miller and Whittier reported nausea in one of the 98 patients treated. Other investigators have reported anorexia, abdominal pain and diarrhea. We have seen one case with "burns" about the anus following therapy.

Oil of chenopodium is effective against *Ascaris* but it is also quite toxic. Its use is limited to those instances where the cost of hexylresorcinol is prohibitive. Craig and Faust state that a combination of chenopodium and tetrachloroethylene (0.3 cc of

oil of chenopodium and 2.7 cc of tetrachloroethylene for adults) is both safe and efficient and recommend this mixture for therapy.

Obstructive symptoms from ascariasis, whether ensuing spontaneously or resulting from improper treatment, have been managed successfully with belladonna morphine, paraffine oil and oil enemas.

Ascaris eggs may be passed in the feces for several days after elimination of adult worms. Brown records the passage of worms for 10 days after treatment. The feces should be examined 2 weeks after treatment and the presence of eggs at that time indicates failure of therapy. Craig and Faust state that it is safe to repeat hexylresorcinol therapy after 3 days. *Ascaris* larvae migrating through the body will be unaffected by the treatment.

Prevention *Ascaris* infections are acquired by the ingestion of eggs from polluted soil. The eggs require at least 8 days to become infective after they have been passed in the feces. The eggs remain viable longest in a light soil in a shady place. There is evidence that the ova may remain viable in such locations for several years, even surviving freezing winter temperatures.

The disease often occurs in cities because of "dooryard pollution" where children may contaminate the soil in play areas. Areas suspected of fecal contamination should be spaded up in order to decrease the chances of ingestion of the eggs. Feces should be disposed of in a sanitary manner and children should be trained not to defecate where soil contamination will constitute a hazard.

FREDERICK J. BRADY

REFERENCES

- Brown, H. W. Intestinal Parasitic Worms in the United States. *JAMA* 103:651, 1934.
 Craig, C. F. and Faust, E. C. *Clinical Parasitology*, Ed. 4. Philadelphia: Lea & Febiger, 1945.
 Eunhorn, N. H., Miller, J. F. and Whittier, L. Ascariasis: Clinical Survey of 125 Cases of Infection with *Ascaris lumbricoides* in Children. *Am J Dis Child* 69:237, 1945.

ENTEROBIASIS (Pinworm Infections)

chan

dren among whom Cram claims that as many as 50 per cent have been found to be infected in some studies. The pinworm has a peculiar life cycle in that the gravid female crawls out of the anus deposits up to 10 000 eggs on the perianal region and dies. Jones and Jacobs report that eggs become infective in about 6 hours and may live for several weeks depending on such factors as temperature and humidity. According to Nolan and Reardon the eggs become distributed throughout the household even being carried about by air currents. Thus despite the usual sanitary precautions the eggs can reach the mouth of the host. Hatching occurs in the upper part of the gastrointestinal tract and development takes place in the intestine. There is no multiplication; the intensity of the infection depends upon the number of eggs ingested.

Two important considerations are frequently overlooked in treating cases for pinworm infection. First, pinworm infection is often familial. Generally all members of a household except small infants are infected some continuously and some intermittently. Therefore the treatment of one member who is known to have the disease is only temporarily successful because he may be reinfected following the migration of a worm from a lightly infected individual. For this reason it is recommended that all household members over one year of age be treated simultaneously in spite of lack of evidence that they are infected. The second important consideration is that treatment must be extended over an interval long enough to allow eggs in the household to become noninfectious before the completion of therapy. A 23 day interval has been sufficient in our experience to accomplish this objective.

We note and it is a common and old story.

which will prevent staining from the dye and probably lessens the gastrointestinal irritation. The tablets are available in $\frac{3}{16}$ and $\frac{1}{2}$ grain sizes. A useful rule in calculating dosage is to give one tablet of the $\frac{3}{16}$ grain size daily for each year of apparent age or one tablet of the $\frac{1}{2}$ grain size daily for each 3 years of apparent age. The maximum dose per day is six $\frac{1}{2}$ grain tablets for adolescents and adults. The tablets are given before

meals; the total number of tablets to be given each day is divided into two or three doses. Thus for adults 2 of the larger tablets are given before each meal.

The schedule of therapy calls for two courses of 8 days separated by a 7 day interval. Therefore the treatment takes 23 days.

Patients should be warned not to chew the gentian violet tablets because of the

usual side effects are due to local irritation. These effects are nausea, vomiting, abdominal pain and diarrhea. With advent of these symptoms the dosage can be reduced to about two thirds of the prescribed amount and therapy continued. Sometimes it may be necessary to discontinue the gentian violet for several days and then to continue with the smaller doses. In such cases it is wise to continue the gentian violet over a longer interval until the total prescribed amount is taken. Uncommonly vertigo and lassitude occur presumably from absorption. Serious organic disease of the liver and kidneys have been considered contraindications to gentian violet therapy. Alcoholic drinks are forbidden lest they increase the absorption of gentian violet.

The treatment of small children who cannot swallow the tablets is not satisfactory. If the child cannot be trained to take the tablets without crushing them in the mouth it is necessary to resort to the use of enemas for therapy. Enemas probably act by mechanically flushing out the more mature worms and it is doubtful that the addition of medicaments has any advantage over saline enemas. Whatever enema is used it should be given nightly at the hour of sleep for the same 23 day interval that the remainder of the household is taking gentian violet.

It is a common and old story.

die undisturbed.

Phenothiazine has been used for treatment of pinworm infections by a number of investigators with success equal to that of gentian violet. Phenothiazine has the dis-

ment is not recommended in these cases but the feces should be examined over a period of several months, because of the possibility of immature worms being present when the first worm was passed

Occasionally in the United States, and frequently in some other parts of the world, patients will be found to harbor hundreds of ascarides. It is in these cases that care must be exercised in selecting an anthelmintic that will rapidly paralyze or kill the ascarides rather than stimulate them, because intestinal obstruction may result in the latter case (see Hookworm Therapy)

Chemotherapy The drug of choice for the treatment of ascariasis is hexylresorcinol. The drug is available in gelatin covered pills (caprokol pills, Sharp and Dohme) containing 0.2 gm of hexylresorcinol. A light meal is given on the evening preceding treatment, breakfast is omitted, and the full dose is given at one time. The adult dose is 5 pills (1.0 gm of hexylresorcinol) with proportionately lesser doses for children to a minimum of 2 pills (0.4 gm) for children under 6 years of age. Brown recommends 0.1 gm for each year of age up to 10 years. Following the administration of the drug, food is withheld for 4 to 5 hours. A saline cathartic is given at 4 to 24 hours after therapy in order to expel the worms. Patients can ordinarily remain ambulant during treatment.

Hexylresorcinol pills should be swallowed without rupturing the coating, otherwise "burns" of the oral mucosa will result. The use of alcoholic beverages during therapy is contraindicated because hexylresorcinol is especially soluble in alcohol, other fluids may be given freely. Gastro enteritis and peptic ulcer are usually considered contraindications to therapy with hexylresorcinol.

Orally administered hexylresorcinol has little toxicity. Einhorn, Miller, and Whittier reported nausea in one of the 98 patients treated. Other investigators have reported anorexia, abdominal pain, and diarrhea. We have seen one case with "burns" about the following therapy

of chenopodium is effective against but it is also quite toxic. Its use is limited to those instances where the cost of hexylresorcinol is prohibitive. Craig and Einhorn state that a combination of chenopodium and tetrachloroethylene (0.3 cc of

oil of chenopodium and 2.7 cc of tetrachloroethylene for adults) is both safe and efficient, and recommend this mixture for therapy.

Obstructive symptoms from ascariasis, whether ensuing spontaneously or resulting from improper treatment, have been managed successfully with belladonna, morphine, paraffine oil, and oil enema.

Ascaris eggs may be passed in the feces for several days after elimination of adult worms. Brown records the passage of worms for 10 days after treatment. The feces should be examined 2 weeks after treatment and the presence of eggs at that time indicates failure of therapy. Craig and Faust state that it is safe to repeat hexylresorcinol therapy after 3 days. Ascaris larvae migrating through the body will be unaffected by the treatment.

Prevention Ascaris infections are acquired by the ingestion of eggs from polluted soil. The eggs require at least 9 days to become infective after they have been passed in the feces. The eggs remain viable longest in a light soil in a shady place. There is evidence that the ova may remain viable in such locations for several years, even surviving freezing winter temperatures.

The disease often occurs in cities because of "dooryard pollution" where children may contaminate the soil in play areas. Areas suspected of fecal contamination should be spaded up in order to decrease the chance of ingestion of the eggs. Feces should be disposed of in a sanitary manner and children should be trained not to defecate where soil contamination will constitute a hazard.

FREDERICK J. BRADY

REFERENCES

- Brown, H. W. Intestinal Parasitic Worms in the United States. *JAMA*, 103:651, 1934.
 Craig, C. F., and Faust, E. C. *Clinical Parasitology*, Ed. 4 Philadelphia: Lea & Febiger, 1945.
 Einhorn, N. H., Miller, J. F., and Whittier, L. Ascariasis. Clinical Survey of 125 Cases of Infection with *Ascaris lumbricoides* in Children. *Am J Dis Child*, 69:237, 1945.

ENTEROBIASIS

(Pinworm Infections)

Pinworm infections are more common than generally realized. Usually the highest incidence is encountered in school-age children.

dren among whom Cram claims that as many as 50 per cent have been found to be infected in some studies. The pinworm has a peculiar life cycle in that the gravid female crawls out of the anus deposits up to 10 000 eggs on the perianal region and dies. Jones and Jacobs report that eggs become infective in about 6 hours and may live for several weeks depending on such factors as temperature and humidity. According to Nolan and Reardon the eggs become distributed throughout the household even being carried about by air currents. Thus despite the usual sanitary precautions the eggs can reach the mouth of the host. Hatching occurs in the upper part of the gastrointestinal tract and development takes place in the intestine. There is no multiplication; the intensity of the infection depends upon the number of eggs ingested.

Two important considerations are frequently overlooked in treating cases for pinworm infection. First pinworm infection is often familial. Generally all members of a household except small infants are infected some continuously and some intermittently. Therefore the treatment of one member who is known to have the disease is only temporarily successful because he may be reinfected following the migration of a worm from a lightly infected individual. For this reason it is recommended that all household members over one year of age be treated simultaneously in spite of lack of evidence that they are infected. The second important consideration is that treatment must be extended over an interval long enough to allow eggs in the household to become noninfectious before the completion of therapy. A 23 day interval has been sufficient in our experience to accomplish this objective.

Wright and Brady recommend as the drug of choice gentian violet given orally. The use of a coating such as the en seals coating (Lilly) will prevent staining from the dye and probably lessens the gastrointestinal irritation. The tablets are available in $\frac{1}{4}$ and $\frac{1}{2}$ grain sizes. A useful rule in calculating dosage is to give one tablet of the $\frac{1}{4}$ grain size daily for each year of apparent age or one tablet of the $\frac{1}{2}$ grain size daily for each 3 years of apparent age. The maximum dose per day is six $\frac{1}{2}$ grain tablets for adolescents and adults. The tablets are given before

meals; the total number of tablets to be given each day is divided into two or three doses. Thus for adults 2 of the larger tablets are given before each meal.

The schedule of therapy calls for two courses of 8 days separated by a 7 day interval. Therefore the treatment takes 23 days.

Patients should be warned not to chew the gentian violet tablets because of the

usual side effects are due to local irritation. These effects are nausea vomiting abdominal pain and diarrhea. With advent of these symptoms the dosage can be reduced to about two thirds of the prescribed amount and therapy continued. Sometimes it may be necessary to discontinue the gentian violet for several days and then to continue with the smaller doses. In such cases it is wise to continue the gentian violet over a longer interval until the total prescribed amount is taken. Uncommonly vertigo and lassitude occur presumably from absorption. Serious organic disease of the liver and kidneys have been considered contraindications to gentian violet therapy. Alcoholic drinks are forbidden lest they increase the absorption of gentian violet.

The treatment of small children who cannot swallow the tablets is not satisfactory. If the child cannot be trained to take the tablets without crushing them in the mouth it is necessary to resort to the use of enemas for therapy. Enemas probably act by mechanically flushing out the more mature worms and it is doubtful that the addition of medicaments has any advantage over saline enemas. Whatever enema is used it should be given nightly at the hour of sleep for the same 23 day interval that the remainder of the household is taking gentian violet.

There is little evidence that hygienic measures alone can control pinworm infections. It may even be possible that vigorous house cleaning stirs up ova that would otherwise die undisturbed.

Phenothiazine has been used for treatment of pinworm infections by a number of investigators with success equal to that of gentian violet. Phenothiazine has the advan-

1 advantage that it is more toxic than gentian violet, and may cause hemolytic anemia. Toxic effects may persist after withdrawal of the drug. Its general use is not recommended at this time.

PREVENTION The usual method of introduction of pinworms into a household is unknown but because of the greater incidence in preschool and school age children these groups are probably responsible for its introduction. Presumably small children in close contact in play and sleep acquire the infection from one another. Adults are likely to lose their infections spontaneously unless in household contact with infected children. Cases should be treated, play habits conducive to transmission should be altered and bad hygienic practices such as biting the fingernails should be discouraged.

FREDERICK J BRADY

REFERENCES

- Cram E H. Studies on Oxyuriasis. Summary and Conclusions. *Am J Dis Child* 65:46 1943.
D'Antonio J S and Sawitz W. Treatment of Oxyuriasis. *Am J Trop Med* 20:377 1940.
Jones M F and Jacobs L. Studies on Oxyuriasis. Survival of Eggs of *Enterobius vermicularis* under Known Conditions of Temperature and Humidity. *Am J Hyg* 33: 1941.
Kuitunen Ekbaum E. Phenothiazine in Treatment of Enterobiasis. *Canad J Pub Health* 37:103 1946.
Nolan M O and Reardon L. Studies on Oxyuriasis. Distribution of Ova of *Enterobius vermicularis* in Household Dust. *J Parasitol* 25:173 1939.
Wright W H and Brady F J. Studies on Oxyuriasis. Efficacy of Gentian Violet in Treatment of Pinworm Infestation. *JAMA* 114:861 1940.

TRICHINOSIS

If it were possible to establish the diagnosis of trichinosis early in the disease the elimination of some worms from the intestine by frequent saline purges might result at least in a lessening of the severity of the acute period. However trichinosis cannot be diagnosed

at this time except under unusual instances. No specific drug has been found to be effective against the worms in the intestinal mucosa or against the circulating and tissue invading larvae. Treatment in the acute episode has been found to be merely palliative.

Prevention Trichinosis results from the

ingestion of viable larvae in meat from hogs, beef, or certain other mammals. Because the infection is acquired from meat, herbivorous animals do not become infected in nature. Pork is the usual source of the infection for man. It is important therefore to cook or prepare pork products so that any larvae present will be killed. Under Federal meat inspection regulations any pork customarily eaten without further preparation by the housewife is processed to kill larvae and is safe. Such preparations not coming under the jurisdiction of the Federal system may or may not be so processed dependent on state and local regulations. Pork should be cooked so well that all parts of the meat reach a temperature of 130° F. A temperature that will change the color of the meat from red to gray. The practice of raising swine on

disease from the country

FREDERICK J BRADY

ANCYLOSTOMIASIS

(Hookworm Infection)

There are two species of hookworm that mature in man: *Necator americanus* and *Ancylostoma duodenale*. The latter is often called the Old World hookworm and it is not known to be endemic in the United States although it is being found in veterans who acquired it during World War II. *A. duodenale* is more pathogenic and less amenable to treatment than *N. americanus*. A differentiation cannot be made by the ova but must be made by examination of the adults.

As with other intestinal parasitic infections attention must be given to emptying the gastrointestinal tract before administering the specific therapy. Saline purges are used because of the solubility of the anthelmintics in oily substances. On the evening before treatment a light meal is given followed by an enema or saline purge. The drug is administered on the next morning without breakfast although fluids are allowed. Another saline purge is given with the anthelmintic or following the drug.

The safety of the drugs used against hookworms is dependent on their lack of

solubility in water and their inability to be absorbed through the intestinal wall

Drugs TETRACHLOROETHYLENE Tetrachloroethylene is the drug of choice for the treatment of hookworm infections. The patient should be hospitalized on the evening

0.1 to 0.2 cc for each year of apparent age

Side effects such as drowsiness, vertigo and vomiting may occur with treatment. Alarming drowsiness is combated by hastening evacuation of the tetrachloroethylene with saline cathartics and enemas.

Liver disease is considered to be a contraindication to tetrachloroethylene although liver damage has not been reported from the use of therapeutic doses. Other contraindications are gastroenteritis, alcoholism, severe malnutrition, severe anemia and a history of having had treatment with heavy metals such as arsenic and mercury. The presence of *Ascaris* ova in the feces is a contraindication to tetrachloroethylene therapy because ascarides stimulated by the drug may cause intestinal obstruction if enough are present.

Tetrachloroethylene is effective in removing hookworms but the treatment often has to be repeated to remove all. A duodenal present. In many veterans several courses of treatment were necessary to remove all of the worms present. In one series only 55 per cent were freed of ova in the feces after two treatments. Treatment with tetrachloroethylene should not be repeated within 10 days.

Tetrachloroethylene is available in capsules from several drug firms. Broken capsules should be discarded.

Occasionally patients are treated en masse for hookworms. Liquid medicinal tetrachloroethylene may be used, the drug being dispensed directly into the dose of magnesium citrate by pipette. Because tetrachloroethylene may oxidize to phosgene on exposure

to air, bottled tetrachloroethylene should be shaken with sodium bicarbonate solution in a separatory funnel before use. The phosgene will be removed with the aqueous phase.

HEXYLRESORCINOL. Patients may be treated with hexylresorcinol without hospitalization. The drug is administered as for *Ascaris* infections. The drug will remove only about one half to two thirds of the hookworms present and for that reason it is less desirable than tetrachloroethylene. Some worms will not be removed and the only criterion for effectiveness in light infections is by the use of quantitative egg counts such as the Stoll count performed before and after treatment.

OTHER CHEMOTHERAPEUTIC AGENTS. Sometimes because of the lack of availability of tetrachloroethylene and hexylresorcinol, other drugs must be used for treatment. These drugs have less of a margin of safety and are not generally recommended. They are given in divided doses after preparation of the patient. Thymol has been used for many years and has been given in doses of 4 gm for adults. Oil of chenopodium has had a wide acceptance and is given in a dose of 1 to 2 cc. Carbon tetrachloride was the precursor of tetrachloroethylene for hookworm therapy and is equally effective but considerably more toxic; the usual dose is 3 cc for adults.

Severe Hookworm Disease. The severity of hookworm disease is roughly proportional to the number of hookworms present. Thus, with only a few worms, no clinical manifestations of the disease will be evident. In heavy hookworm infestation the manifestations may be associated with severe anemia, severe malnutrition, weakness and apathy. Such cases are poor risks for anthelmintic therapy. Effort should be made to correct the anemia and malnutrition. The patient is put to bed and given a balanced diet supplemented with vitamins and massive doses of iron. Transfusions may be necessary. After the patient has improved with this regimen, specific anthelmintic therapy can be given. Hexylresorcinol is recommended for the first treatment in these cases.

Creeping Eruption. In addition to two species of hookworms mentioned, man is also subject to transient infection with hookworms of dogs and cats.

Ancylostoma braziliense of the southern states. In the skin these larvae produce "creeping eruption" and they may even play a role in the production of Löffler's syndrome. These larvae in the skin produce tortuous elevated linear lesions that are intensely pruritic. The larvae move a few millimeters to a few centimeters each day and remain alive for several months. Freezing the area with ethyl chloride or solid carbon dioxide has given the most consistent beneficial results. Fuadin (see Schistosomiasis) has been claimed to be beneficial but Dolce and Franklin observed improvement in only 3 of 14 patients.

Prevention. Hookworms are acquired by contact with soil previously contaminated with the eggs. The eggs hatch and the larvae develop to the infectious stage in a few days; these larvae are motile and can even climb up on moist blades of grass. The larvae penetrate the skin on contact and after a complex migration through the tissues reach the intestinal lumen. Therapy is directed against the adults in the intestine; no drug is known to be effective against the migrating forms of the hookworm in humans. The eggs and larvae survive best in moist shady places where the soil is a sandy loam.

Preventive measures include the therapy of known cases and the avoidance of soils that might be contaminated. Shoes should be worn in suspected areas. Promiscuous defecation is an important factor in maintaining the infection in the soil. Prevention in endemic areas is also a sanitation problem for public health agencies. Education of school children as to the dangers of hookworm disease and how to prevent it is valuable. Attempts may be made to alter the habits of natives who perpetuate the disease. The best permanent measure lies in the installation of safe privies or sewer systems and teaching the residents to use these facilities. The use of human excrement for fertilizer, as practiced in many countries needing a rigid economy, is a source of hookworm infection for which no satisfactory control measure has been found at the present time.

"Creeping eruption" is acquired in areas where infected dogs and cats have defecated. These places may be under sheds in the woods and frequently on beaches. Where the disease exists, dogs should be frequently

treated for hookworm infections; avoidance of contact of skin with soils that might be infected is recommended.

FREDERICK J. BRADY

REFERENCES

- Dolce F. A. and Franklin J. E. Creeping Eruption. Results of Treatment with Fuadin. *Arch. Dermat. & Syph.* 52:174, 1945.
 Hitch J. M. Systemic Treatment of Creeping Eruption. *Arch. Dermat. & Syph.* 65:664, 1947.
 Most H., Hayman J. M. Jr. and Wilson T. H. Hookworm Infections in Troops Returning from the Pacific. *Am. J. M. Sc.* 212:347, 1946.
 Wright D. O. and Gold E. M. Löffler's Syndrome Associated with Creeping Eruption (Cutaneous Helminthiasis). Report of 26 Cases. *Arch. Int. Med.* 75:303, 1946.
 Wright W. H. Treatment of Some Intestinal Worm Infections. *Am. Pract.* 1:589, 1947.

FILARIASIS

(Bancroft's Filariasis)

Two filarial parasites of man, *Wuchereria bancrofti* and *Wuchereria malayi*, cause similar clinical manifestations. The disease is called filariasis or better Bancroft's filariasis. The disease can be classified into three clinical types: (1) cases with microfilariae in the peripheral circulation but without symptoms; (2) cases with intermittent acute symptoms such as lymphadenitis and lymphangitis with or without microfilariae in the blood; and (3) cases with late sequelae such as chyluria or elephantiasis with or without microfilariae. The available evidence indicates that the microfilariae play no part in the production of symptoms; the manifestations are due to the presence of adult worms and in some cases to concomitant bacterial infection.

The objectives of therapy must be under-

of microfilariae has been used as the criterion of efficacy of chemotherapeutic agents. Within recent years several drugs have been shown to eliminate microfilariae. Adequate time has not elapsed to determine the effects of these drugs on adult worms and on the symptoms.

Three types of compounds have been shown to eliminate microfilariae in Bancroft's

filariasis These are antimonials arsenicals and one recently tested piperazine derivative hetrazan (Lederle) The effects of these compounds on adult worms are known only by inference because of the difficulty in recovering mature worms Scanty evidence is available indicating that the compounds alleviate the acute attacks of filariasis

Chemotherapy Although antimonials given parenterally have been used for many years in the experimental therapy of filariasis only in recent years has their action been unequivocally demonstrated Brown used a trivalent antimony compound (antihomaline Merck) and found that the number of microfilariae was rapidly reduced during treatment and that they even disappeared from the blood in several cases Culbertson Rose and Oliver Gonzalez used a pentavalent compound (neostibosan Winthrop) which caused a slow drop in the numbers of microfilariae and in a years interval about half of their treated patients were microfilaria free Both groups of investigators had inferential evidence that the adults were affected by the treatment and subsequently antimony compounds have been shown to affect the adults of a filarial parasite of dogs In general the reactions with antihomaline were more severe than reactions to neostibosan

Thetford Otto Brown and Maren reported their results with the use of a phenyl arsine oxide (arsenamide) administered intravenously in 6 cases showing microfilariae There was a rather prompt reduction or disappearance of the microfilariae noted at the end of treatment Reactions to the drug were mild The authors believe that the adult worms were affected on the basis of febrile reactions and eosinophilia during treatment and local reactions in 2 patients probably at the site of adult worms

Santiago Stevenson Oliver Gonzalez and Hewitt treated 26 cases with hetrazan (1 diethylcarbonyl-4 methyl piperazine hydrochloride) This organic compound was effective in reducing the number of microfilariae within one day when given orally in doses of 0.5 to 2 mg per kilogram of body weight three times daily Observations made up to 5 months after treatment showed reduced numbers of microfilariae in all patients and some were freed of circulating microfila-

riae Reactions to the drug were mild with fever leukocytosis and eosinophilia in most patients Four patients had a localized lymphadenitis that the authors attributed to injury to adult worms

It may be said that three different types of drugs are known to affect the microfilariae and there is indirect evidence that all have an effect on the adult worms The value of these drugs for relief of symptoms is not entirely clear Thetford et al cite the case of a patient with scrotal swelling hydrocele enlargement of femoral and inguinal nodes and brawny edema of the right leg These symptoms were presumably due to filariasis although microfilariae were not observed

No report has indicated that the use of the drugs mentioned above has any unfavorable effect upon the disease by accelerating the development of sequelae

It is considered advisable to use a microfilaricidal drug in case of filariasis both because of a possible favorable effect on the symptoms and because of the reduction of numbers of microfilariae with decreased danger of mosquito transmission Of the drugs that have this action hetrazan is safest and easiest to administer

Other than the somewhat empirical use of a drug the treatment of the acute episodes of lymphangitis and lymphadenitis and of the subacute and chronic sequelae is palliative In cases in which secondary bacterial invasion may be present penicillin or sulfa drugs should be given Plastic operations have been developed for treating elephantiasis they are most successful in scrotal elephantiasis

Prevention The disease can be prevented either by avoidance of the bites of the mosquito vector or by reducing the microfilaria level in the human hosts The vectors of filariasis breed and remain close to human habitations Hence an infected individual may serve as the reservoir from which he himself is repeatedly reinfected It is important therefore to the patient as well as to his neighbors that the microfilariae be eliminated Thus the measures used for other mosquito transmitted diseases are applicable such as sleeping under bed nets, DDT spray

ing and eradication of mosquito breeding places. Large scale treatment of microfilaria carriers probably will result in decreased chances of infection if carried out over a period of time.

FREDERICK J BRADY

FILARIAE OTHER THAN BANCROFT'S FILARIASIS

In addition to human infections with filaria of the genus *Wuchereria* infections occur with *Onchocerca volvulus*, *Loa loa*, *Mansonella ozzardi*, and *Acanthocheilonema perstans*. Because the latter two parasites are non pathogenic, they will not be discussed.

Onchocerciasis Onchocerciasis differs from the other human filariae in that the microfilariae are found in the skin, and the adults are localized in subcutaneous nodules. The late sequela of blindness is probably due to cumulative injury from microfilariae in the eye, the adults cause no other symptom than the production of nodules.

Until 1947, the only treatment was the surgical removal of nodules with the hope that the numbers of microfilariae would be decreased. In 1947, Van Hoof, Henrard Peel, and Wanson showed that suramin (Bayer 205 or naphuride sodium, Winthrop) eliminated the microfilariae and killed the adult *Onchocerca*. Mazzotti and Hewitt in 1948 reported that hetrazan (Lederle) reduced the numbers of microfilariae. Further observations on the use of both drugs were made by Burch.

Suramin is administered intravenously at weekly intervals in 1 gm doses for adults for 8 weeks. The optimal dosage for hetrazan is not established, Burch used up to a total of 46 mg per kilogram of body weight over a 3 week interval. The drug is given orally in two or three daily doses.

Burning of the feet was the only important reaction attributed to the suramin per se and no reaction was attributed to hetrazan. With either drug however, severe reactions sometimes occurred, apparently due to the tissue reaction from dead and dying microfilariae. These reactions were mainly ocular, as photophobia, lacrimation, burning and itching, and skin reactions such as pruritus, induration, and edema. In general, hetrazan produced more severe side effects

than suramin but with both drugs the severity was correlated with the degree of the infection. The reactions from hetrazan ensued promptly after a single dose of the drug, the reactions from suramin came on more gradually after four to six injections.

its in Af

rica and in limited areas in Central America. The disease is transmitted by small biting gnats. Protection is based on the use of insect repellents applied to the skin, pyrethrum sprays for quick "knock down," and application of DDT to surfaces where the insects may rest. Large scale eradication of breeding places has not been practical, in spite of the fact that larval stages of the insect are susceptible to the action of DDT.

Loiasis Adult *Loa loa* migrate through the subcutaneous tissue, and their migrations are probably related to a syndrome called Calabar swelling, similar to angioneurotic edema. The adult worms sometimes may be seen migrating across the eye beneath the conjunctiva. The microfilariae are found in the blood and probably are innocuous.

The adult worms may be removed surgically while migrating across the eye. Preliminary reports indicate that hetrazan may be effective against the microfilariae.

PREVENTION Loiasis occurs in Africa and it is not uncommon in returned missionaries. The disease is transmitted by a biting fly about the size of the housefly and is related to deer flies. The insects usually bite out doors during daylight hours. Presumably, the use of newer repellents on the skin will deter them from biting.

FREDERICK J BRADY

REFERENCE

- Brown, H. W. Treatment of Filariasis (*Wuchereria bancrofti*). *JAMA* 125:952, 1944.
Burch, T. A. Experimental Therapy of Onchocerciasis with Suramin and Hetrazan. *Bol. Ofic. San. panam.* 28:233, 1919.
Culbertson, J. T., Rose, H. M., and Oliver, Gonzalez, J. Chemotherapy of Human Filariasis by the Administration of Neostibosan. *Am. J. Trop. Med.* 25:403, 1944.

Mazzotti, L., and Hewitt, R. I. Tratamiento de la oncocercosis por el cloruro de 1-diethylcarbamyl-4-methylpiperazina (Hetrazan) *Medicina, México*, 28 30, 1948

Santiago-Stevenson, D., Oliver Gonzalez, J., and Hewitt, R. I. Treatment of *Filariasis bancrofti* with 1 diethylcarbamyl 4 methylpiperazine Hydrochloride (Hetrazan) *Ann New York Acad Sc*, 50 161, 1948

Thetford, N. D., et al. Use of a Phenyl Arsenoxide in the treatment of *Wuchereria bancrofti* Infection *Am J Trop Med*, 28 577, 1943

Van Hoof, L., et al. Sur la chimiothérapie de l'oncocercose, note préliminaire *Ann soc belge med trop*, 27 173, 1947

GUINEA WORM INFECTION

The female guinea worm (*Dracunculus medinensis*) when mature is about 1 meter in length. It is observed clinically as a long tortuous elevation of the skin, usually of the lower extremities, generally superficial, particularly over bony prominences. The male worms probably lie deep in the tissues and are not demonstrated clinically.

When the female has matured, it migrates to the skin and the head of the fully developed female worm becomes located under a blister that forms on the skin. This blister ruptures when it comes in contact with water, thereby liberating embryos. The live worm *in situ* produces little reaction unless there is secondary infection or rupture or death of the worm. These complications may cause considerable disability owing to inflammation and scarring, sometimes interfering with locomotion by involvement of muscles, tendons, or joints. Treatment is directed at the removal of the female worm.

The treatment of antiquity was slowly delivering the worm from the tissues by rolling a short length daily onto a split stick until it is completely removed. Medical science has improved considerably on the treatment of the ancients with a similar method. After the blister is formed, the area is exposed to fresh water in a basin and the developed embryos escape. Using an aseptic technique, the head is exposed and secured to the skin

and a dressing applied. Each day thereafter, the delivered part of the worm is again exposed to fresh water to empty the uterus.

gentle traction can be exerted on the worm lest it be broken within the tissues, giving rise to complications. Other disadvantages of this method are that considerable time is required (since the adult female is about 1 meter in length and only 1 or 2 cm can be delivered daily) and secondary bacterial infection may occur.

Operative removal is sometimes under-

ing the extraction.

Elliott has described a method using intramuscular injections of an oily emulsion of phenothiazine near the site of the worm. He injects as much as 4 gm of phenothiazine at one sitting, and gives injections at weekly intervals. At 5 to 7 days after the first injection, extraction is started and as much as 1 foot of the worm may be removed at once. Even if no worm is presenting, the induration resolves and the sinuses dry in 10 to 14 days.

Prevention. Important foci of the disease exist in Asia and Africa, but there are also a few small foci in Central and South America. Infestation has been reported only in animals within the United States. The disease is acquired from drinking water containing Cyclops infected with the parasite. Cyclops are removed from our waters by sand filtration, and chlorine presumably kills larvae and adults, so that little danger of human infection exists where water supplies meet our present-day standards.

FREDERICK J. BRADY

REFERENCE

Elliott, M. *New Treatment for Dracunculiasis*. *Tr Roy Soc Trop Med & Hyg*, 35 291, 1942

DISEASES OF METABOLISM

DIABETES MELLITUS

Four different sets of conditions should be recognized in the treatment of proved diabetes mellitus. They are

- (1) Mild diabetes manageable by restriction of food
- (2) Severe forms of the disease requiring adjunctive use of insulin routinely
- (3) Acidosis and other acute complications such as infection and surgical or traumatic events
- (4) Chronic complications particularly those of vascular origin

Each of these requires specific methods of treatment suitable for the class and varying only in detail. The first three demand regulation of the disordered state of carbohydrate metabolism. With proper understanding effective control of them can be accomplished with diet alone, diet together with insulin or insulin together with supplementary measures. In the fourth class regulation of the carbohydrate metabolism is advisable but often ineffective. Other medical measures are required but even so progress of the complication often cannot be stopped.

Criteria for Good Control Most authorities agree that it is desirable to control abnormal hyperglycemia and glycosuria as far as possible without unendurable inconvenience to the patient and danger of severe shock from insulin. In some instances these two qualifications make it advisable to permit minimal or transient glycosuria as the lesser of two evils. But with proper care the majority of diabetic patients can be maintained in approximately normal sugar balance without either of these penalties. This should be done whenever possible. The necessity for condoning some glycosuria in certain cases should not be permitted to encourage laxity of control in the majority. Established criteria for good routine management consists of the maintenance of normal nutrition and as good control of

abnormal blood and urine sugar as possible without more serious penalties. The following description of therapeutic methods is based on this principle.

Mild Diabetes. DIETARY CONTROL. Probably about half of all proved uncomplicated cases of diabetes mellitus can be managed by restriction of the food intake. These patients usually are obese in middle or advanced age, not diabetic for long and have not suffered from the disease. They do not show excessively high sugar levels and develop acidosis only when acute complications exist. They have never used insulin or have used it only temporarily. When these characteristics are present an effort to manage the diabetes by diet should always be made and will often be successful. Loss of excess weight is usually advisable in addition. Diet restriction therefore is doubly important. The use of insulin may prevent loss of weight by encouraging greater food consumption.

Three types of diet are suitable for this class of patients. The last two are also appropriate for maintenance of normal nutrition even though insulin is required.

Desugarizing. When abnormal glycosuria and hyperglycemia exist when the patient uses no insulin and when no acute infection or ketonuria is present desugarization by diet is indicated.

A desugarizing diet is one which will support normal weight at minimum activity, will maintain protein balance, will not cause ketonuria and will supply adequate accessory elements such as bulk, minerals, vitamins and water. It must be as low as possible in glucose value without conflicting with those requirements. (If body weight is excessive it may also be restricted in calories below a maintenance level by reduction of its fat content. In that case the total calories required for maintenance must be calculated according to the methods described below with subsequent arbitrary reduction of the fat. This insures freedom from ketosis.)

Calories From 20 to 35 calories per kilo gram of body weight per day are required for maintenance of weight at minimum activity.* Older and inactive persons require less, young and active persons more. An average allowance for an older individual weighing 140 lbs would be $110 \text{ kg} \times 25$ calories or 1575 calories per day.

Protein About 1 gm of protein per kilo gram of body weight per day is ordinarily adequate to preserve nitrogen balance and other needs for protein in adults.* The average person selected above would therefore, need about 63 gm of protein daily. This would yield 252 calories daily. Deducted from the total caloric requirement (1575 - 252), this leaves 1323 calories to be supplied by carbohydrates and fat.

Carbohydrate-Fat Ratio When the fat supply is much more than double the carbohydrate, ketosis is likely to occur. Yet the carbohydrate must be as low as possible without ketosis, in order to accomplish de-

* Children require as much as double these amounts.

sugarization. Ratios of about 1:2 in grams ($2C = F$) are most desirable in desugarizing diets. In the example given above, 1323 calories must come from carbohydrates and fat, or $4C + 9F = 1323$. If $2C = F$, $4C = 2F$. Therefore, $2F + 9F = 1323$ and $F = 120$. By selection the carbohydrate is one half the fat, in this case 60.

The fuel values for this desugarizing diet are thus C-60, F-63, F-120, C-109, Calories 1572. Children and people of greater or lesser weights and degrees of activity can be supplied by similar simple calculations.

Food Prescription Table I gives this example of a desugarizing diet in detail. For obvious reasons, bread and other starchy foods should be omitted from the selection. The form employed shows the percentage composition of the common foods used. It includes the calculations involved in supplying the required fuel values. Table II shows the choice of individual foods from each group. Better training is provided and greater accuracy insured if the patient is re-

TABLE I
DESUGARIZING DIET*

Standard Foods		Grams of Foods Permitted at Each Meal			Daily Totals--Fuel Values			
See Groups for Selection	G	Morning	Noon	Night	24 Hours	C	F	P
Vegetable	4		200	200	400	16	4	0
Fruit	8	100		100	200	16	2	0
Bread	20							
Meat	16		50	50	100	0	25	15
Eggs	4	2			2	0	12	12
Milk	7	100	100	100	300	15	0	12
Cream	0	100	100	100	300	15	9	60
Butter	0	10	10	10	30	0	3	25.5
G Per Meal		34	34	42	Total	62	61	124
Height		66*	4xC		243	1xC	62	
Weight		140	4xP		244	0.58xP	35.4	
Ideal Weight		140	9xF		1116	0.10xF	12.4	
Caloric Requirement		1575	Calories		1608	Glucose	110	

* See footnote, Table II

TABLE II
STANDARD FOOD GROUPS *

Foods listed in groups below may be selected in any combination according to amounts specified in diet requisition			
Vegetable (Fresh cooked or canned without added sugar)	Asparagus Celery Lettuce Endive Chard Watercress Radishes Pickles	Cauliflower Cabbage Sauerkraut Brussels Sprouts Summer Squash Artichokes Okra Eggplant	String Beans Wax Beans Cucumbers Tomato Spinach Beet Greens Broccoli Onion
Fruit (Fresh cooked or canned without added sugar)	Oranges Grapefruit Lemons Limes	Strawberries Cantaloupe Honeydew Watermelon	Canned Fruits (4 10% C) Gingerale
Bread (Weigh before toasting)	White Rye Whole Wheat	Corn Bread Graham Bran Bread	Rolls (Plain) Biscuits Buns
Meat (Free from excess fat Weigh after cooking)	Beef Lamb Mutton Veal Pork Ham Bologna Frankfurters	Chicken Turkey Duck Goose Tongue Liver Sweetbreads Kidney	Fish Lobster Crabmeat Shrimps Scallops Cottage Cheese
Milk	Whole Milk		
Cream	20 per cent Cream Sour Cream		Olives Avocados
Butter (and other fats)	Butter Oleomargarine Meat Fat Cod Liver Oil		French Dressing Mayonnaise Salad Oil

* Reprinted from *Diabetes Mellitus in General Practice* by Arthur R. Colwell 1947 (courtesy of The Year Book Publishers 304 S Dearborn St Chicago)

quired to weigh the diet for a practice period at least rather than use household measures. When this is impossible the diet may be transposed into estimated portions by reference to Table III.

The variety afforded by the substitution list shown in Table IV is sufficiently desirable to warrant the use of food scales and the metric system.

Additions When a desugarizing diet is in effect the elevated blood and urinary sugar may either disappear or level off above normal. In the former case cautious additions should be made, preferably in the form of carbohydrate foods, for greater palatability,

to provide more calories for greater activity and to reduce the chances of ketosis in case of unavoidable glycosuria. Additions that can be made without return of abnormal blood and urinary sugar levels are advantageous. If sugar reappears the need for insulin is established. Methods for using it will be considered in a subsequent section. Additions to the food supply can be made after desugarization by insulin.

Maintenance When desugarization has been accomplished, either by diet or by the adjunctive use of insulin, a diet is required which is capable of supporting normal weight and health at the optimal activity

TABLE III
APPROXIMATE WEIGHT IN GRAMS OF COMMON PORTIONS OF FOOD*

<i>Vegetables</i>	<i>Fruits</i>
200 gm	200 gm
1 Glass Juice	1 Glass Juice
1 Head Lettuce Endive	1 Large Apple
1 Bowl Soup	100 gm
1 Large Tomato	1 Saucedish Cooked Fruit
100 gm	$\frac{1}{2}$ Medium Grapefruit or Melon
1 Sauce dish Cooked Vegetable	1 Large Peach
1 Small Tomato	1 Medium Apple or Orange
10 Brussels Sprouts	$\frac{1}{2}$ Large or 1 Small Banana
1 Small Glass Juice	3 Halves Cooked Apricot
50 gm	50 gm
5 Radishes	1 $\frac{1}{2}$ Slices Pineapple
3 Stalks Celery	$\frac{1}{2}$ Cup Berries
4 Small Pickles	3 Prunes
1 Medium Dill Pickle	15 Grapes
<i>Cooked Cereals and Starches</i>	<i>Breads and Flour Products</i>
100 gm	50 gm
$\frac{1}{2}$ Cup Gruel or Porridge	1 Large Roll or Muffin
$\frac{1}{2}$ Cup Cooked Rice or Cereal	1 8" Waffle
$\frac{1}{2}$ Cup Macaroni or Spaghetti	1 4" Pancake
2 6" Ears Corn	1 Doughnut
1 Medium Potato	20 gm
$\frac{1}{2}$ Cup Mashed Potato	1 Slice Bread
1 Saucedish Cooked Vegetable	1 Small Roll
50 gm	4 Soda Crackers
1 Small Potato	2 Rye Krisp
$\frac{1}{2}$ Medium Sweet Potato	8 10 Potato Chips
<i>Meats and Cheese</i>	<i>Milk Cream and Fats</i>
200 gm	200 gm
1 Large Steak	1 Glass Milk or Cream
100 gm	100 gm
1 Broiled Chicken	1 Small Glass Milk or Cream
1 Medium Hamburger	$\frac{1}{2}$ Cup Ice Cream
2 Frankfurters	20 gm
$\frac{1}{2}$ Cup Salmon	2 Tbsp Cream
5 Oysters	2 Links Pork Sausage
4 Tbsp Cottage Cheese	4 Strips Bacon
50 gm	1 Tbsp Peanut Butter
2 Small Lamb Chops	10 gm
1 Loin Pork Chop	1 Pat Butter
1 Slice Bologna	1 Tbsp Salad Dressing
10 Shrimps	6-10 Shelled Nuts
$\frac{1}{2}$ Pkg Cream Cheese	2-3 Olives
1 Thick Slice Cheese	

* See footnote Table II

TABLE IV
SUBSTITUTION FOOD GROUPS *

Standard Foods in these amounts 100 gm <i>Vegetable</i>	May be exchanged for other foods in these amounts			
	Carrots Beets Turnips Rutabagas Standard Fruits	50 gm Mushrooms Peppers Pumpkin Kohlrabi		30 gm Peas Parsnips Catsup Horseradish
100 gm <i>Fruit</i>	Apples Pears Peaches Apricots	60 gm Raspberries Blackberries Blueberries Loganberries	Cherries Pineapple Canned Fruit (11 15% C)	40 gm Bananas Plums Grapes Prunes Cooked Figs Fresh
20 gm <i>Bread</i>	60 gm (cooked wt) Corn Potato Baked Squash Baked Beans Lima Beans Macaroni Spaghetti Noodles	35 gm (cooked wt) Baked Potato Sweet Potato	Rice Barley Oatmeal Cornmeal Flour Farina Hominy Popcorn	15 gm (dry wt) Corn Flakes Wheat Flakes Rice Flakes Shredded Wheat Cream of Wheat Pretzels Crackers Rye Krisp
25 gm <i>Meat</i>	50 gm Oysters Clams Frog Legs Milk Buttermilk	20 gm Cheese American Brick Swiss Cream		One Egg
One Egg	50 gm Oysters Clams Frog Legs Milk Buttermilk	Meat Poultry Fish Liver Tongue	25 gm Lobster Shrimp Crabmeat Scallops Cottage Cheese	20 gm Cheese American Brick Swiss Cream
50 gm <i>Milk</i>	50 gm Buttermilk Skim Milk	25 gm Evaporated Milk		10 gm Condensed Milk Cocoa (dry wt)
50 gm <i>Cream</i>	25 gm Cocoanut (fresh) Whipping Cream	15 gm Shelled Nuts Peanut Butter Shredded Cocoanut		10 gm Bitter Chocolate
10 gm <i>Butter</i>	20 gm (cooked wt) Bacon Pork Sausage	50 gm Cream = 50 gm Milk and 8 gm Butter		

* See footnote, Table II

required by the patient. This must be as convenient and palatable as possible within the limitations imposed by the necessity for controlling the sugar balance and maintaining uniformity and accuracy of treatment. Conservative rules for the selection of such a diet may be outlined as follows:

Calories. Age and activity are the most important factors governing the selection of a maintenance diet. Adults usually require from 25 to 40 calories per kilogram per day. Lower amounts are needed by older and sedentary persons and more by the young and active. Heavy manual laborers and children may demand as many as 50 calories per kilogram. Thin people and men need more, women and obese persons less. An average allowance for a young 160 lb. adult would be $75 \text{ kg} \times 35 \text{ calories} = 2625 \text{ calories}$.

Protein. At least 1 gm. of protein per kilogram per day is necessary for maintenance of normal nutrition. There is seldom any harm in giving more. Children need fully

360 calories, leaving 2160 to be supplied by carbohydrate and fat.

Carbohydrate-Fat Ratio. Ratios of less than 1

impose more generous amounts of carbohydrates and are more difficult to balance with or without insulin. They are, therefore, not used by the author except when special indications exist.

Conservatism dictates that a ratio of 1.1 to 3.2 in carbohydrates to fat in grams is most desirable. In the example chosen above

2160, $F = 166$ and C also is 166, since by selection, it is equal to F .

A maintenance diet for this person, therefore, contains fuel values of $C = 166$, $P = 90$ and $F = 166$, $G = 235$, Calories 2518. It should be noted that the glucose value of this diet is more than double that of the desugarizing diet selected in the previous section, because of its higher ratio and the greater size and activity of the patient for whom it was planned.

Food Prescription. Table V gives the detailed kinds and amounts of common foods used in the fulfillment of these fuel requirements and their distribution into meals. Tables II, III, and IV provide data making it possible to enjoy variety of selection and to avoid weighing foods, if desired, by conversion of the diet into measured equivalents.

Weight Reduction. Either the desugarizing type of diet or the maintenance diet can be modified for purposes of reducing weight when required.

Reducing diets are planned in exactly the same manner as described for desugarization and maintenance but the fat content is decreased arbitrarily after planning the food values to a level which will impose a caloric deficit. This forces the combustion of stored fats in amounts which approximate the deficit, and preserves the total exogenous and endogenous fat combustion at the level and ratio planned originally, thereby insuring freedom from ketosis.

In the example of a maintenance diet described in the preceding section arbitrary reduction of the fat from 166 gm. to 40 gm.

imposed because the total calories are reduced from 2520 needed for maintenance to 1384. Restrictions of the carbohydrate could impose a greater deficit and more rapid weight reduction although only about 330 additional calories could be eliminated in this way (without creating ketogenic conditions by lowering the ratio to less than 1.2).

When the patient is overweight the diet should be planned as if the excess weight were to be maintained and the fat reduced secondarily. This avoids prescription of diets which are accidentally ketogenic or sub-maintenance in protein. When the patient is underweight or normal the diet should be planned to maintain the ideal weight, because excess calories and protein can do no harm.

Insulin Requirements. When dietary adjustment fails to produce good control of abnormal glycosuria and hyperglycemia without nutritional penalties, the routine use of insulin becomes necessary. The need for it

TABLE V
MAINTENANCE DIET *

Standard Foods		Grams of Foods Permitted at Each Meal				Daily Totals—Fuel Values			
See Groups for Selection	G	Morning	Noon	Night	10 P M	24 Hours	C	P	F
Vegetable	4		200	200		400	16	4	0
Fruit	8	150	150	150		450	36	45	0
Bread	58	40	40	40	40	160	84.8	14.4	3.2
Meat	16		50	100		150	0	37.5	22.5
Eggs	4	2				2	0	12	12
Milk	7		200		100	300	15	9	12
Cream	9	100		100	100	300	15	0	60
Butter	11	20	20	20	5	65	0	6	55.9
G Per Meal		55	69	72	40	Total	167	91	185
Height		70	4 x C		668	1 x C		167	
Weight		160	4 x P		364	0.58 x P		50.8	
Ideal Weight		160	9 x F		1485	0.10 x F		165	
Caloric Requirement		2520	Calories		2517	Glucose		236	

* See footnote Table II

usually is permanent although borderline cases in which its temporary use permits good control later without it are not infrequent. On this account insulin should always be urged rather than to allow even minimal hyperglycemia. There are more important considerations than freedom from diabetic symptoms chiefly those of islet damage and danger of infectious and vascular complications from persistent hyperglycemia.

ACTION OF INSULIN AND ITS MODIFICATIONS

To understand the proper use of various in-

lin preparations, the most commonly used modifications is essential.

All insulin preparations are virtually ineffective when given by any other route than parenterally. They are almost always given hypodermically. Each patient must be instructed in the technique of the hypodermic injection. Figure 1 shows the method of administration taught by the writer. A 1 cc

syringe graduated into tenths and a 27 gauge 1½ in stainless steel needle are preferred.

Unmodified Insulin. Regular insulin (solution of amorphous insulin) and crystalline insulin (solution of zinc insulin crystals) are almost identical in action. The effects of single large doses on glycemia and glycosuria are shown in Fig. 2 in contrast with those of the most commonly used depot preparation protamine zinc insulin. Their action is prompt, reaching a peak in about 4 hours, intense and fairly brief, exhausting their effect in about 12 hours. For these reasons these unmodified preparations are most useful in emergencies and to supplement the depot insulins. In routine treatment they must be injected more than once daily (sometimes every 6 hours or so) in order to provide overlapping effect. For routine use they have been largely replaced by depot insulins with more sustained, less intense action.

Because their absorption rates do not de-

pend on any depot principle the unmodified insulins are more uniform and dependable in effect than the longer acting preparations. This is decidedly advantageous in the extremely severe labile forms of diabetes seen chiefly among children and young adults where minor variations in the intensity of insulin effect often result in gross changes toward hypoglycemia or hyperglycemia.

Protamine Zinc Insulin This is the most commonly used depot preparation. It is a suspension of amorphous crystals of insulin precipitated in combination with a mono protamine (salmine) and zinc in a neutral aqueous vehicle. Correct dosages are obtained only by thorough mixing of the suspension in its vehicle. After hypodermic injection insulin is released from its slowly soluble combination with the protamine and zinc probably by enzymatic action. This is the "depot" effect.

Gradual weak and prolonged reduction

beyond 24 hours daily injections overlap each other in effect with the result that the response to any given daily dosage is not seen for several days. Accordingly the response to changes or omission of its daily administration is not seen for days for the same reason.

Protamine zinc insulin is most useful in less severe forms of diabetes in which details of insulin timing are relatively unimportant and weak insulin effect is all that is required. This may be true even when large daily doses are required owing to "insulin insensitivity" or relative refractoriness for any reason.

Insulins with Intermediate Action During recent years some refinements in effective insulin therapy have become possible as a result of the development of insulin modifications with time action intermediate between those of unmodified insulin and the original depot preparation protamine zinc insulin. Neither the fast nor the slow acting standard insulin fits the needs of the patient with severe diabetes very well. Ordinary insulin must be injected several times daily. Even then its effect wanes so rapidly in severe diabetes that hyperglycemia and glycosuria occur during the hours of sleep even

without food. At the other extreme protamine zinc insulin is so weak and prolonged in effect that dosages sufficiently large to control the glycosuria which follows the meals are likely to cause severe insulin shock during hours of fasting, especially during sleep. In the past it has often been supplemented by separate injections of regular insulin for this reason. Small amounts of regular insulin added to larger amounts of protamine zinc insulin are precipitated by the excess protamine present and lose their identity.

Globin insulin with zinc is the only intermediate insulin sold at the present time. It is an acid aqueous solution of insulin in combination with beef globin and zinc. It is partially precipitated after injection hence it has both a rapid and sustained effect. It is more rapid and less prolonged in action than protamine zinc insulin but less rapid and intense and decidedly more prolonged in action than unmodified insulin. The average response to a single large dose is shown in Fig. 3 in comparison with two commonly used protamine insulin mixtures. In Fig. 2 contrasts of its effects with those of similar single doses of ordinary and protamine zinc insulin are demonstrated.

Protamine insulin mixtures containing excesses of unmodified insulin also possess time action of an intermediate character. Thorough mixtures containing about twice as much regular or crystalline as protamine zinc insulin fit the needs of most severe diabetic patients. Occasionally the mixtures must contain three times as much regular insulin as protamine zinc insulin for best results. There is not much difference in the responses to single doses of globin insulin and a 2:1 mixture. Probably the latter preparation permits greater overlapping of depot effect in single daily dosage. A 3:1 mixture is decidedly more intense and less prolonged than either of the others. The mixtures are compared graphically in Fig. 3 in contrast with the fast and slow effects of ordinary and protamine insulin shown in Fig. 2.

These intermediate insulins are most appropriate when diabetes is so severe that (1) fasting glycosuria and hyperglycemia follow the use of ordinary insulin, (2) postcibal glycosuria occurs with amounts of protamine insulin sufficiently large to control fasting hyperglycemia, (3) nocturnal hypo-

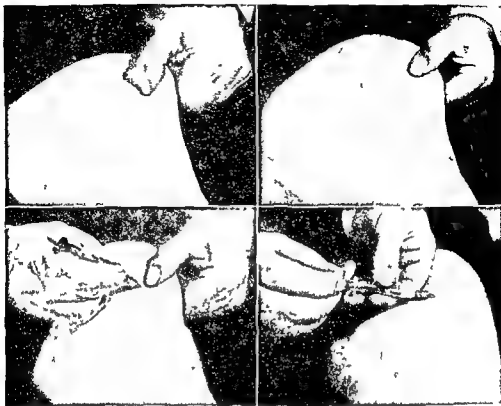


Fig 1 Technic of insulin injection (see footnote Table II)

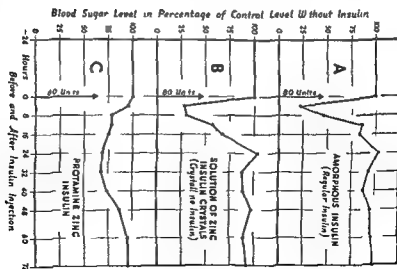


Fig 2 Action curves of large single doses of standard insulins (see footnote Table II)

DISEASES OF METABOLISM

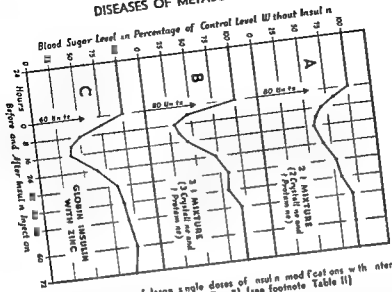


Fig 3 Action curves of large single doses of insulin preparations with intermediate timing (compare with Fig 2) (see footnote Table II)

glycemia and insulin shock are caused by amounts of protamine zinc insulin large enough to control glycosuria following meals. They are almost always used in single daily doses before breakfast in the morning.

There is not much choice between globin insulin and insulin mixtures. The chief advantage of the former is the fact that it can be used as marketed. The mixtures must be prepared in the ampule or syringe from market supplies of their component parts. They possess the advantage of greater elasticity for individual needs by change in proportions. Greater overlapping of effect from the 2:1 mixture is also desirable in some patients. The choice between them depends on their appropriateness as determined by actual trial and comparison in individual patients.

A suspension of protamine insulin crystals containing about 40 per cent as much protamine as standard protamine zinc insulin ("NPH50") possesses time activity comparable to those of the 2:1 mixture and globin insulin with zinc.

INSULIN IN SEVERE DIABETES. As indicated above, diabetes is not infrequently so severe that rapid shifts in sugar balance occur with insulin preparations which do not efficiently fit the feeding and fasting needs of the patient. About one-half of all insulin-treated patients fall into this category. Diabetes has existed for a long time or which

has developed early in life almost always behaves this way. Special insulin techniques are then required for best results. Selection of the most appropriate insulin often makes the difference between good health and some degree of disability.

The most common pattern in diabetes of this type is as follows. Without insulin glycosuria is intense, symptoms severe, and acidosis extremely likely to occur. With ordinary insulin, daily multiple injections are required for good control, including one during the normal hours of sleep. Fasting hyperglycemia is high unless a substantial dose of one of the depot insulins is used, or ordinary insulin is given during the night. Protamine insulin in dosage great enough to reduce the early morning sugar level to normal permits heavy glycosuria to follow meals and yet is likely to cause nocturnal hypoglycemia. The insulin requirement commonly ranges from 40 to 60 units daily, although exceptions may occur in insulin-sensitive individuals.

Diabetes so severe that these characteristics are present requires one of the depot insulins with intermediate action. Globin insulin or one of the protamine insulin mixtures containing at best twice as much insulin as protamine insulin often corrects the faults in the timing of the standard preparations.

Globin insulin may stop both the postprandial glycosuria and nocturnal hypoglycemia and yet preserve an approximate

normal fasting level. It may cause insulin reactions at the time of its peak action (8 to 16 hours after injection) or permit slightly high early morning levels, owing to inadequate overlapping. In that event the slightly less intense, more prolonged action of a 21 mixture is preferable.

INSULIN IN DIABETES OF MODERATE SEVERITY When reduction of the food supply fails to control abnormal glycosuria and hyperglycemia and yet diabetes is judged not to be severe, moderate doses of protamine zinc insulin are preferred. Daily injections before breakfast are given.

Dosages required usually range from about 10 to 40 units daily. Much more may be required by insensitive patients even when their diabetes is inherently not severe.

When the diet has been set at a maintenance level which is not extravagant in carbohydrate and blood and urine sugar levels are persistently high a daily trial dose of protamine zinc insulin should be injected, preferably for about one week, and the response observed. The fasting blood sugar concentration before breakfast measures this response most specifically because it determines the peak action of the depot effect and warns of impending hypoglycemia. Postprandial and 24 hour glycosuria should also be observed because they may indicate the need for one of the intermediate depot insulins.

Adjustment of the dosage of protamine zinc insulin should be made (ordinarily at intervals of not less than 3 or 4 days) until the early morning blood sugar level is approximately normal. If no glycosuria then occurs at any time of day, the balance may be considered satisfactory. Gradually progressive lowering of the fasting sugar level may then follow, owing to slowly accumulating depot effects, exercise, or improvement in severity of the diabetic process. This requires subsequent reduction in dosage and may allow withdrawal of all insulin and satisfactory control by diet alone.

If any glycosuria follows meals in spite of the attainment of normal or subnormal fasting sugar levels with protamine zinc insulin, redistribution of the food or insulin is necessary. When the disproportion between the day and night sugar levels is not great, correction of both is sometimes possible by

transfer of carbohydrate foods from meal time to a lunch at bedtime. The total carbohydrate of the diet can be reduced with the same result, along with a reduction in the size of the dose of protamine zinc insulin.

When the amount of glycosuria following meals is great or the nocturnal hypoglycemia severe, protamine zinc insulin should be discontinued and one of the intermediate depot preparations substituted.

On the other hand, if either of these insulins permits afternoon or evening glycosuria to occur in spite of daily doses large enough to reduce nocturnal glycemia to normal, an insulin with even more rapid action is required. A mixture containing two and one half or even three times as much regular insulin as protamine insulin is then needed. Diabetes of this type is unusual.

INSULIN IN LABILE ("BRITTLE") DIABETES A good many young (and some older) patients with diabetes of long standing exhibit a pattern which defies almost all attempts at perfect control of glycosuria without insulin shock. On ordinary programs of management they behave unpredictably. A constant diet and insulin regimen permit sudden and unexpected shifts in glycemia from one extreme to the other for no apparent reason. These patients accept large waves of glycosuria alternating with severe insulin reactions with resignation and concern. Their number is increasing because of the lengthened life and greater duration of diabetes of young people with the disease.

A satisfactory balance is difficult to secure for these patients and sometimes impossible. Ordinarily some degree of glycosuria must be accepted as the lesser of two evils, the other being frequent insulin shock. Compromise with ordinary standards of control is inevitable in some cases. The most satisfactory criteria for treatment involve (1) maintenance of normal nutrition, (2) freedom from diabetic symptoms and all ketonuria, (3) elimination of severe reactions from insulin, (4) as little glycosuria as possible without great inconvenience in the diet or insulin routine.

With presently available methods of treatment two specific plans are most satisfactory. Both take advantage of the fact that insulin modifications with sustained action are unpredictable in their intensity of overlapping.

normal fasting level. It may cause insulin reactions at the time of its peak action (8 to 16 hours after injection) or permit slightly high early morning levels, owing to inadequate overlapping. In that event the slightly less intense, more prolonged action of a 2:1 mixture is preferable.

INSULIN IN DIABETES OF MODERATE SEVERITY When reduction of the food supply fails to control abnormal glycosuria and hyperglycemia and yet diabetes is judged not to be severe, moderate doses of protamine zinc insulin are preferred. Daily injections before breakfast are given.

Dosages required usually range from about 10 to 40 units daily. Much more may be required by "insensitive" patients even when their diabetes is inherently not severe.

When the diet has been set at a maintenance level which is not extravagant in carbohydrate and blood and urine sugar levels are persistently high, a daily trial dose of protamine zinc insulin should be injected, preferably for about one week, and the response observed. The fasting blood sugar concentration before breakfast measures this response most specifically, because it determines the peak action of the depot effect and warns of impending hypoglycemia. Postprandial and 24 hour glycosuria should also be observed because they may indicate the need for one of the intermediate depot insulins.

Adjustment of the dosage of protamine zinc insulin should be made (ordinarily at intervals of not less than 3 or 4 days) until the early morning blood sugar level is approximately normal. If no glycosuria then occurs at any time of day, the balance may be considered satisfactory. Gradually progressive lowering of the fasting sugar level may then follow, owing to slowly accumulating depot effects, exercise or improvement in severity of the diabetic process. This requires subsequent reduction in dosage and may allow withdrawal of all insulin and satisfactory control by diet alone.

If any glycosuria follows meals in spite of the attainment of normal or subnormal fasting sugar levels with protamine zinc insulin, redistribution of the food or insulin is necessary. When the disproportion between the day and night sugar levels is not great, correction of both is sometimes possible by

transfer of carbohydrate foods from meal time to a lunch at bedtime. The total carbohydrate of the diet can be reduced with the same result, along with a reduction in the size of the dose of protamine zinc insulin.

When the amount of glycosuria following meals is great or the nocturnal hypoglycemia severe, protamine zinc insulin should be discontinued and one of the intermediate depot preparations substituted.

On the other hand, if either of these insulins permits afternoon or evening glycosuria to occur in spite of daily doses large enough to reduce nocturnal glycemia to normal, an insulin with even more rapid action is required. A mixture containing two and one half or even three times as much regular insulin as protamine insulin is then needed. Diabetes of this type is unusual.

INSULIN IN LABILE ("BRITTLE") DIABETES A good many young (and some older) patients with diabetes of long standing exhibit a pattern which defies almost all attempts at perfect control of glycosuria without insulin shock. On ordinary programs of management they behave unpredictably. A constant diet and insulin regimen permit sudden and unexpected shifts in glycemia from one extreme to the other for no apparent reason. These patients accept large waves of glycosuria alternating with severe insulin reactions with resignation and concern. Their number is increasing because of the lengthened life and greater duration of diabetes of young people with the disease.

A satisfactory balance is difficult to secure for these patients and sometimes impossible. Ordinarily some degree of glycosuria must be accepted as the lesser of two evils, the other being frequent insulin shock. Compromise with ordinary standards of control is inevitable in some cases. The most satisfactory criteria for treatment involve (1) maintenance of normal nutrition, (2) freedom from diabetic symptoms and all ketonuria, (3) elimination of severe reactions from insulin, (4) as little glycosuria as possible without great inconvenience in the diet or insulin routine.

With presently available methods of treatment two specific plans are most satisfactory. Both take advantage of the fact that insulin modifications with sustained action are unpredictable in their intensity of overlapping.

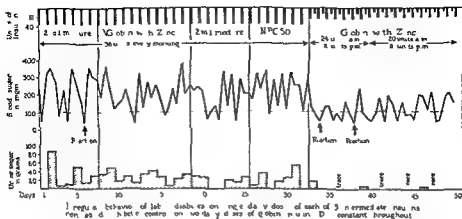


Fig 4 Irregular behavior of labile diabetes with one dose daily of various intermediate insulins. Improved control when one of them was given twice daily (see footnote Table II)

effect. Modifications with more rapid action injected more frequently distribute their available insulin more uniformly and efficiently.

The most effective but also most inconvenient of these plans involves the injection of unmodified insulin three or four times daily including an injection during the hours of sleep. Four doses of equal size given at approximately 6 hour intervals along with feedings of equal value are capable of yielding good control even in the most difficult patients of this type. (The fact that this is possible appears to prove that the unpredictable behavior is due to inconstant rates of insulin release inherent in all depot insulins given at longer intervals.) The regimen is so arduous that few patients can adhere to it for long. The two nighttime doses may be replaced by one dose of an intermediate preparation with less inconvenience but also with less consistent control.

The most satisfactory plan (which compromises between convenience and perfect control) involves the use of one of the intermediate insulins twice daily. Figure 4 shows the improved control secured in one brittle case when this technic was substituted for one larger dose given once daily.

Specifically the method requires that the total daily insulin dose be divided into a larger dose (two thirds to three-quarters of the total) before breakfast and a smaller dose (from one third to one-quarter of the total) at bedtime along with a small lunch.

Shifts in balance are minimized by this method. Slightly smaller amounts of insulin are needed probably because of greater efficiency. The exact timing of the insulin is not important provided one of the intermediate modifications is used. The effect of the morning dose is judged by the sugar levels in the late afternoon and evening; that of the night dose by the levels before and after breakfast. Redistribution of food improves the results after uniform patterns of

insulin effect exceeds the available supply of sugar for any reason signs of insulin shock appear. In diabetes this happens most frequently when dosage is too high or distributed improperly when absorption of depot insulin is accelerated (as by accidental injection into a vein) when diabetes is unproved after injection or as a result of treatment or when food is delayed, reduced or vomited. It also occurs commonly when exercise improves sugar utilization or accelerates release of insulin from injection depots. It is always annoying, sometimes alarming and rarely fatal. In moderate severity it may lead to mental irresponsibility and physical incoordination simulating drunkenness and thus be the cause of violent accidents especially in driving an automobile.

TIME. Each type of insulin has its own characteristic time for insulin shock to result

Unmodified insulin causes shock about 3 to 5 hours after injection intermediate preparations such as globin insulin and protamine insulin mixtures in about 8 to 16 hours and protamine insulin during the longest period of fasting usually during the night. With any type of insulin exercise increases the chances of shock especially during the late afternoon. Reactions seldom occur within 2 or 3 hours immediately following the ingestion of food. These rules of timing frequently are useful in distinguishing insulin reactions from other suspicious phenomena.

SYMPTOMS In its mildest form insulin shock is characterized by hunger, weakness, and trembling. Children are unaccountably fretful. Unreasonable behavior and failure to recognize the cause of the symptoms are common. In a more advanced stage there is gray pallor, profuse perspiration, incoordination, and silly or sullen behavior. Diplopia and numbness of the tongue or lips may be present. In this stage physical accidents may occur owing to poor judgment and incoordination. Alcoholic intoxication may be suspected. The most severe stage resembles an epileptic seizure. Unconsciousness, rigidity, and convulsions are characteristic. The patient is usually in a cold sweat, breathing is stertorous, and efforts to arouse him are unsuccessful. Labile diabetes may pass into this stage with no warning. Sleeping subjects may be discovered in that condition probably because earlier symptoms were unrecognized during sleep.

When unconsciousness due to insulin shock has persisted a long time, residual mental and physical symptoms may continue even after normal sugar levels have been restored. Prolonged stupor is the ordinary residue, but abnormal personality changes, motor signs, and even psychotic behavior may occur. These sequelae are probably due to cerebral damage. When they occur they are confusing because the usual favorable response to administered sugar is masked thus raising doubt about the diagnosis.

DIAGNOSIS Severe insulin shock is easily distinguished from diabetic coma by its rapid onset, absence of air hunger, ordinarily sugar-free and ketone-free urine, low blood sugar, and normal plasma carbon dioxide combining power. It is not so easy to distinguish from head injury, apoplexy, epi-

lepsy, and myocardial infarction with unconsciousness due to shock. Blood sugar analysis settles the diagnosis if quickly available. If not, and even though the urine contains sugar, intravenous injection of glucose is indicated immediately for differentiation. Usually failure to improve promptly rules out insulin shock if sufficient glucose is given.

TREATMENT Treatment consists of giving enough sugar to stop the symptoms and signs. In mild reactions this can be accomplished by feeding fruit juice, sugar candy, or milk until recovery is complete. Ten to 20 gm of carbohydrate are practically always sufficient even in severe shock. During unconsciousness swallowing may be impaired and oral feedings aspirated into the respiratory system. It should be tested with small amounts of water and food withheld if doubtful. Epinephrine hypodermically followed by sugar by mouth or glucose by vein in 10 to 20 gm amounts are then preferred and rapidly effective.

Although it is not possible to avoid insulin reactions in any patient who uses the hormone, most of them can be prevented by the consistent application of a few simple rules. The patient must eat his prescribed food on time, not increase insulin unless it is indicated unequivocally, take extra carbohydrate during unaccustomed exercise, and not ignore mild symptoms of hypoglycemia. With depot insulins, occasional fasting blood sugar estimations warn when dosage is excessive. The physician must know how the effect of depot preparations is distributed, respect their cumulative effect when used initially, watch for signs of improving tolerance during effective treatment, and after complications adjust the food intake in such a manner that the danger of hypoglycemia is

— Most important when instability
1st pre
choice
must be made between the two evils of inter-

be condoned in minimal amounts necessary to avoid insulin shock.

Acute Complications The most effective
1st not acute

baste is essential. Acute illness puts sugar metabolism out of control; this in turn, aggravates the illness, which again affects the diabetes adversely. The vicious cycle thus initiated by acute disease cannot ordinarily

last a variety of them. This value may be lowered or raised, if desired, for any given patient, but it should be maintained at a uniform level, both day and night, after it is selected in any one case, unless insulin shock demands extra sugar temporarily.

TABLE VI

PARENTERAL AND ORAL FEEDINGS EACH OF 40 GM GLUCOSE VALUE, FOR USE EVERY SIX HOURS IN EMERGENCY MANAGEMENT *	
800 cc 5 per cent glucose	400 cc 10 per cent glucose
800 cc 5 per cent amino acids in 5 per cent glucose	400 cc orange or grapefruit juice
600 gm milk	250 gm milk
2 eggs	250 gm cream
200 gm milk	40 gm bread
200 gm cream	10 gm butter
30 gm crackers or dry cereal	200 gm milk
100 gm milk	1 egg
100 gm cream	40 gm bread
150 gm fruit †	150 gm milk
15 gm dry cereal	1 egg
100 gm cream	40 gm bread
100 gm milk	10 gm butter
100 gm fruit †	50 gm meat or cheese
2 eggs	20 gm bread
20 gm bacon	10 gm butter
40 gm bread	150 gm fruit †
5 gm butter	100 gm cream
100 gm meat	100 gm vegetable †
200 gm vegetable †	20 gm bread
20 gm bread	10 gm butter or dressing
10 gm bread or dressing	100 gm milk
50 gm cream	100 gm cream
	100 gm fruit †

* See footnote Table II

† Selected from "Standard Food Groups" shown in Table II

frequent intervals must be applied.

Acute diseases which frequently demand vigorous treatment by quickly effective methods are acidosis, acute infection, surgical interference, and trauma. All of these except severe forms of acidosis can be managed easily by a rational method of using ordinary insulin. The treatment of precomatose and comatose states will be considered separately.

SIX HOUR EMERGENCY MANAGEMENT
When heavy glycosuria with or without ketonuria, exists as a result of any acute illness, it can be eliminated within 24 hours as a rule, by judicious adjunctive use of ordinary insulin.

It may be used in mild acidosis without symptoms during acute infection if the sugar balance is disturbed before surgery if quick control is essential, and after operations, anesthesia or severe injury which

about 6 hours after each of these feedings, (3) injections of unmodified insulin every 6 hours, after each test and before each next feeding; the size of each dose determined by the response to the previous injection. Figure 1 outlines the methods in diagrammatic form.

Feedings. In order that the supply of sugar may be constant and therefore, ignored as a possible variable affecting the sugar balance, a meal, series of feedings, or parenteral injection of uniform glucose value is given every 6 hours throughout each 24 hour period. For adults, feedings of 40 gm of glucose value are most convenient. Table VI

The alimentary capacity of the patient naturally determines the choice of individual feedings. During vomiting and immediately

insulin should be injected at slow rates which will not flood the tissues and

dose can then be given, along with the uniform feedings, as long as the complication exists. Minor adjustments can be made as the insulin requirement changes.

The success of this method of using insulin depends on a number of factors. The sugar supply must be uniform day and night. Trial and error determine the insulin needed by each patient. The 6 hour interval must be maintained continuously for feedings, tests, and insulin. No single dose of insulin can be omitted even if no food is taken without affecting the reliability of the method, because serious dislocation of overlapping effects thereby is introduced. Finally, depot insulins should not be adjusted while this method is in operation. If used previously

not be started until the daily requirement of the patient can be estimated and routine management begun. Their adjustment during emergencies introduces a variable which only makes decisions regarding the 6 hour dosage of supplementary insulin more difficult.

Transfer to Routine Management. Ordinary methods of diet and insulin adjustment as outlined in previous sections can be resumed whenever conditions permit. Before this is done a stable insulin requirement is desirable. The complicating illness should have subsided and the patient's appetite returned to normal.

This conversion can be made by omitting the fourth 6 hour feeding during the night, giving the entire diet in the other three meals (at mealtime instead of 6 hour intervals) and one dose of one of the depot insulins every morning before breakfast. Its size should be a little less than the sum of the 6 hour doses plus any depot insulin used previously. When no depot insulin has been used during the emergency, the regular insulin should be tapered off during the first 2 or 3 days in which the full daily dose of depot insulin is used. Stopping it suddenly

daily depots before effective insulin can be relied upon.

ADVANCED DIABETIC ACIDOSIS (PRECOMATOSE AND COMATOSE STATES) It must be appreciated that the therapeutic methods described in this section are applicable only when ketogenic acidosis exists in an advanced stage. Undoubtedly the most serious emergency caused by diabetes mellitus and usually dramatically responsive to proper treatment, the severe form of acidosis ac-

counts section: Unconsciousness in diabetes caused by complications other than acidosis (viz., cerebral and cardiovascular accidents, trauma, insulin shock, alcohol) should be distinguished carefully from diabetic coma and precoma and treated by appropriate methods. Strenuous therapy, as used for severe acidosis, can be disastrous if applied in mild acidosis or other forms of coma not due to acid intoxication.

In the order of their greatest importance, the useful therapeutic weapons are unmodified insulin in large doses at frequent intervals, parenteral fluids, glucose, salt replacement and plasma and circulatory stimulants on occasion.

Insulin. Only unmodified insulin should be used. Depot insulins serve no useful purpose in the emergency, although there is some advantage in not stopping them if used previously. Ordinary insulin must be given without delay in large doses at intervals of not more than 6 hours. The prompt administration of a decisively large dose often is of lifesaving importance because time runs out. Other agents used in treatment are of no importance if too little insulin is used too late, or if effective insulin is allowed to fade by long intervals between doses.

The size of the initial dosage depends on the size and condition of the patient. In adults with vomiting, moderate breathlessness, drowsiness, and alkali reserve readings in the vicinity of 20 to 30 volumes per cent, an initial dose of 40 to 60 units is indicated. Twice as much should be given initially if extreme air hunger and deep stupor are present and the blood pressure, pulse, and

urine output are not critically affected. True coma usually does not exist up to this stage. After circulatory collapse has begun with cyanosis, coldness, rapid pulse, low blood pressure, oliguria or anuria, and failing respiration, all treatment is usually ineffective unless several hundred units are given immediately, at least half by vein and circulatory efficiency is restored by other supportive measures. In children this suggested dosage scale should be revised according to body weight. If severe infection accompanies advanced acidosis, dosages should be at least doubled.

The only dependable rule dictates that *enough insulin should be given to stop the progress of the acid intoxication without causing violent insulin shock!* Ordinary doses are ineffective and massive doses not to be feared if the patient is critically ill. Insulin shock can be prevented by glucose administration as required, therefore, it is better to err by giving too much rather than too little.

The patient's response to the insulin given initially determines the size of subsequent dosage! If irreversible parenchymatous damage has not occurred, effective insulin is indicated primarily by improvement in respiratory distress in 3 to 5 hours. Abrupt decreases in preceding diuresis and high sugar levels give confirmatory proof of adequate insulin and warn of danger of hypoglycemia. These usually occur later and are of less value as early guides than the rate and depth of breathing. If no improvement is seen within the first 3 to 5 hours, the initial dosage must be considered ineffective and larger amounts given promptly and watched as before. A single large dose is more rapidly effective and more easily evaluated than multiple small doses at short intervals. Under no circumstances should more than 6 hours elapse before additional insulin is given even after massive initial amounts with favorable response.

After improvement occurs an injection of insulin should be given every 6 hours day and night, according to the principles outlined previously for the 6 hour emergency method. A massive dose can be repeated, if seen to be effective, unless excessive polyuria, glycosuria and ketonuria have been observed. Thereafter it can be halved every

8 hours, provided increasing glycosuria does not recur, until ordinary maintenance doses of 50 to 100 units daily (12 to 24 units every 8 hours) prevent excessive glycosuria without causing hypoglycemia. Routine feeding and depot insulin control can then be resumed, as previously described. Patients who have come out of severe acidosis seldom can be maintained on less than 40 units of insulin daily. They usually require more.

Fluids Because of vomiting and diuresis extreme dehydration always exists in advanced diabetic acidosis. Its correction is secondary in importance only to sufficient insulin.

During the first day of treatment at least 3 liters of water must be given to the adult of average size. Four to 6 liters are probably better, although cardiac and gastric dilatation can occur readily by administration rates which are too rapid.

If anuria exists fluids should be given as 5 per cent glucose to protect against insulin shock from large doses. If the urinary output is satisfactory, $\frac{1}{2}$ molar sodium lactate or normal salt (without glucose) can be used as long as heavy glycosuria is known to exist by frequent testing of catheterized specimens. Delay in giving glucose helps to rehydrate the subject more rapidly because glycosuria and diuresis, which are excessive at first, are not increased by glucose which is wasted. Abrupt fall in urinary volume or sugar demands prompt use of glucose solutions to prevent insulin shock.

Not enough fluid can be given in early stages by routes other than parenteral ones because of vomiting and stupor.

Glucose After heavy glycosuria and polyuria decrease as a result of insulin glucose with or without amino acids should be given in solution parenterally until food and fluids can be taken by mouth. About 40 gm every 6 hours represents a useful and convenient rate. It can be increased temporarily if hypoglycemia threatens. It is highly desirable to give enough to reproduce glycosuria when the urine clears suddenly owing to large amounts of insulin. The 40 gm per 6 hour rate can then be resumed when a

Salt Replacement Vomiting and diuresis result in significant losses of mineral elements from the body which must be replaced. Sodium, phosphorus and potassium have been shown to be of greatest importance in this respect.

Sodium should be given in 20 to 40 gm amounts parenterally during the first day as normal saline or $\frac{1}{4}$ molar sodium lactate solution. About 2 gm of potassium should be given in addition if any signs of hypopotassemia exist (extreme muscular weakness, respiratory embarrassment, low blood potassium level). Phosphates are excreted in large amounts in acidosis and are necessary for normal sugar utilization. Probably they should be given routinely along with sodium and water.

Circulatory Support When diabetic subjects in acidosis are first seen late in the course of the acid poisoning, an unavoidably high mortality rate is inevitable. Characteristics of this terminal stage are cyanosis, hypotension, rapid thready pulse, coldness, anuria, shallow respiration and plasma carbon dioxide combining power below 10 volumes per cent. Recovery from this condition is possible only if the shock-like state can be restored toward normal, even though all other methods of treatment are carried out with meticulous thoroughness.

Two or 3 units of blood plasma given intravenously may restore adequate circulation. Other fluids in large amounts are indispensable. External heat should be used. Circulatory stimulants such as caffeine, camphor and even digitalis sometimes appear to help. Epinephrine should not be used. If the circulation cannot be improved by these or other methods, the outcome is usually fatal. In borderline situations in which it can be the use of those methods along with heroic treatment of the acidosis represents the difference between success and failure of treatment.

Chronic Complications Treatment dur-

necessary during chronic disorders which accompany diabetes.

Dietary Adjustments Obesity requires caloric restriction. The detail of this adjustment has been discussed in a previous section. It is of practical importance not only for correction of obesity itself but as a therapeutic aid in the treatment of most cardiac, vascular and hypertensive complications. Certain orthopedic, infectious and vascular defects of the legs and feet require reduction of the weight.

Pregnancy and lactation demand increases in the caloric intake sufficiently great to maintain weight at normal levels.

Chronic infections usually require a greater caloric and protein intake than normal. Both should be increased by 25 to 50 per cent over customary levels. The behavior of the body weight is the most satisfactory measure of the adequacy of the diet. Pulmonary tuberculosis is particularly important in this respect, although the same dietary adjustments are indicated in any chronic infectious disease in which normal nutrition is difficult to maintain.

Protein deficiency states demand specific increases in the diet protein to levels of 15 to 2 gm per kilogram of body weight per day in adults and correspondingly higher amounts in children. This diet correction is applicable in conditions associated with albumin loss, certain types of hepatic disease and anemia in pregnancy after starvation and in hyperthyroidism and chronic infections. Renal insufficiency with nitrogen retention or uremic tendencies demands restriction of the protein to about 0.5 gm per kilogram per day unless hypoproteinemia also exists. In the latter case, the lesser of two evils must be selected.

Carbohydrate increases are indicated occasionally particularly before and after thyroid and biliary tract surgery and after any infectious or malnutrition state which depletes liver glycogen. Carbohydrate to fat ratios double those ordinarily selected should then be used until the deficiency is considered to be corrected.

Gastrointestinal complications generally require appropriate restriction in the selection of food but no change in the fuel value of the diet from those ordinarily used in the treatment of diabetes.

when the two conditions are not associated.

TREATMENT OF DIABETES Certain specific adjustments of the diet and insulin are often

Insulin Adjustments During infections,

Excessive use of coffee, so common with diabetics on restricted diets, should be stopped. None of the vasodilator or sedative drugs interfere with diabetic management, provided they are not dispensed in vehicles containing sugar.

Cardiac Disease In the management of heart disease in diabetic patients obesity frequently requires correction and carbohydrate restriction should not be severe. Bed

amount used under ordinary conditions. Doubling or tripling the dosage is not at all unusual. Daily dosages in the hundreds or even thousands of units are rarely required. "Insulin resistance" (refractoriness insensitivity) is then considered to exist. Correction of abnormally high hyperglycemia and glycosuria by the use of adequate insulin sometimes makes the difference between satisfactory and unsatisfactory progress in the complicating illness, particularly in those of an infectious nature. Late in pregnancy the lowered "threshold" for sugar excretion demands that blood sugar levels be used in measuring the response to increased insulin. Renal glycosuria may be misleading.

Certain chronic complications likewise demand that less insulin than usual be used in diabetes. Obviously any condition which interferes with the customary intake of food will do so. In most cerebrovascular and cardiovascular complications it is prudent to lower insulin dosages cautiously and permit moderate hyperglycemia to exist as a cushion.

sitivity and so reduce the amount of insulin needed, sometimes radically. The termination of pregnancy usually demands rapid reduction in previously increased insulin dosage.

TREATMENT OF COMPLICATIONS Some specific differences in therapy of chronic diseases occurring in diabetic patients deserve special emphasis.

Vascular Disease The management of arterial hypertension in diabetes does not differ from that of hypertension in general. Inasmuch as many older diabetic patients are obese, reduction of weight is one of the few measures which accomplishes anything. None of the other measures usually used in attempts to control hypertension conflict with the treatment of diabetes. Surgery should be performed only under conditions of strict control of hyperglycemia and glycosuria.

tion of normal activity after rest and compensation. Digitalis, quinidine, ammonium chloride, mercurial diuretics, vasodilators, opiates, and barbiturates all are virtually without effect on sugar balance and act the same as in similar nondiabetic conditions.

Polyncuritis In common with practically all neurologic diseases occurring in diabetic patients, the treatment of diabetic polyneuritis is just about as ineffective as anything in the entire field of medicine. Restoration of normal sugar balance does not help and actually may precipitate an attack. Rest and heat are of some value. In severe attacks the only measure which provides substantial relief from pain is the use of sedatives frequently, in large doses, and over considerable periods of time.

Severe attacks of neuritis ordinarily are uninfluenced by vitamin therapy, but large parenteral doses of thiamine chloride should be tried, as occasionally patients are relieved by it. Mild attacks consisting of vague pains in the extremities may be relieved dramatically by vitamin B therapy.

Ocular Complications Transient errors of refraction due to changing water balance in the lens frequently accompany rapid desugarization. The disturbance of vision almost always corrects itself spontaneously in the course of a few weeks with no treatment except maintenance of approximately normal sugar balance. Suitable lenses correct the refractive error temporarily. But it is fruitless to fit lenses at the height of the visual error because it changes quantitatively from day to day owing to constantly changing conditions within the eyeball. The best treatment, if the error is proved to be refractive, is to reassure the patient, do nothing for 2 to 4 weeks, then recheck the eyes on two

type of refractive error, and the difference often is in the direction of normal

The treatment of permanent, mature lens cataracts is the same in the presence of diabetes mellitus as in nondiabetic patients. In expert hands cataract removal is a perfectly safe procedure, provided the diabetes is controlled properly. Because of the frequent association of cataracts and retinal pathology, the condition of the retina should be estimated carefully before removal of the lens. Sometimes the retinal condition cannot be judged because of the cataract. In that case, it seems legitimate to remove one lens, but defer judgment on possible restoration of vision until the retina can be seen.

Glycosuria and excessive hyperglycemia must be corrected preoperatively and postoperatively, according to the principles for any surgical procedure. The lens removal and the postoperative care must be conducted with a minimum of trauma to the eye because of the great danger of hemorrhage due to vascular disease or hypertension or both. During the immediate postoperative period a small margin of hyperglycemic protection against insulin shock is less dangerous than hypoglycemia because of the risk of hemorrhage within the eye. Infection occurs at times. Enucleation is occasionally necessary because of persistent ophthalmitis from hemorrhage or infection. The risks of lens removal for cataract are somewhat greater in diabetic than in nondiabetic patients chiefly for the reasons described.

The treatment of retinitis in diabetes is most unsatisfactory. The value of diets high in protein is suggested by the studies of Schneider, Lewis, and McCullagh with serum proteins in human and experimental diabetes. Vitamin C and rutin should be prescribed, although no uniform improvement has yet been demonstrated due to their use. Occasional patients have improved with

raised blood pressure by any means possible with safety.

The prevention of retinitis and the means of improving it after it has appeared must wait for a better understanding of the reasons for its occurrence in diabetes. Until then every effort should be made to correct known metabolic abnormalities by proved methods of dietary and insulin control. Hypoglycemia should be avoided, of course.

Glomerulosclerosis The treatment of intercapillary glomerulosclerosis is fundamentally the same as that of any form of chronic nephritis. Heavy loss of albumin with hypoproteinemia and edema should be replaced by means of high protein feedings or blood plasma injections. Sodium restriction, acid-ash diets and mercurial diuretics are effective in the relief of edema. Digitalization and bed rest may be required if congestive heart failure on an arteriosclerotic or hypertensive basis accompanies the renal disease,

proteinemia is not present.

Gangrene The treatment of unmistakable dry gangrene is to maintain sterile conditions if possible, protect from injury, swelling, and chilling; use the best of the various methods available for promoting the formation of collateral circulation; watch for suppuration and wait for clear cut demarcation to occur. If the lesion escapes infection and demarcation is satisfactory, amputation at the line of demarcation may be attempted, using great care not to injure healthy tissues proximal to the lesion any more than is necessary. Infection or gangrene of the stump is likely to result from this procedure and it should not be attempted until the tissue proximal to the lesion is in excellent condition.

After amputation the stump should be left open and packed with a water soluble sulfonamide ointment such as sulfa-carbowax (3 per cent sulfathiazole and 1 per cent sulfadiazine in carbowax, a water soluble hydrocarbon ointment base made by the Union Carbide and Carbide Company). A

objectives of treatment is reduction of ele-

Infections The treatment of infected lesions varies somewhat with the detailed conditions present. The procedure of greatest value is continuous warm moist compresses of generous thickness, kept warm with an automatic heat cradle, and not permitted to dry out. For this purpose the most satisfactory technic in the author's experience has been the use of generous thicknesses of soft compress material wrung fairly dry after immersion in saturated aqueous magnesium sulfate solution. A waterproof layer of thin material, such as rubber sheeting or waxed paper, is wrapped around the moist compress and the entire dressing then enclosed snugly in a warm, dry outer dressing to keep it moist and warm. An automatic heat cradle or other device can then be placed over the foot and leg to prevent cooling. The compresses should be changed every 2 or 3 hours. If maceration of the skin occurs, compresses should be discontinued for a day or so. The foot should be elevated and at complete rest.

Next in importance to warm moist heat, elevation, and rest is judicious drainage of suppurating lesions. Whether suppuration occurs superficially in or under the epidermal layer or whether it is in deeper layers of the toe, foot, or leg, it should be drained as promptly as possible, but with a minimum of trauma to uninvolved tissue. When a suppurative cavity with a thin roof can be demonstrated, it should be incised conservatively, necrotic sloughs excised without trauma to adjacent walls, and satisfactory drainage established. Packing the cavity with the chemotherapeutic agents described above, or continued warm, moist compresses should follow incision and debridement. Ordinary surgical principles for suppurative infection should be applied with the additional precaution of extreme care to avoid any injury which is not essential to provide drainage. Sloughs should be allowed to separate rather than cause injury of viable tissues to which they are attached. Drainage should be conservative rather than radical, unless it can be accomplished through necrotic tissues. Moist heat is preferable to dry heat after incision, and absolute rest and elevation of the extremity must be maintained until active granulation and epithelialization begin.

Chemotherapy has become indispensable in the treatment of infected lesions of the extremities in diabetes, with or without gangrene. Penicillin, streptomycin, and the sulfonamides used generally or locally should be selected according to the organism present. The use of chemotherapeutic agents intra-arterially in the affected extremity and by local infiltration into and around the lesion have been reported to be of benefit. It is difficult to maintain effective concentrations by these methods, however, and the latter is theoretically subject to the criticism of causing local trauma and spreading infection.

Amputation is indicated if any of the following sets of conditions are present:

- (1) Rapid extension of infection up the leg in spite of local therapeutic measures, threatening sepsis or metastatic infection.
- (2) Intractable pain of long duration with poor prognosis for the extremity.
- (3) Unsuccessful treatment of a localized lesion with the probability that healing will never occur, osteomyelitis being one of the most common reasons for such lack of progress.
- (4) The probability of a poor functional result even though healing of the lesion can be accomplished.
- (5) Recurrent lesions in the same extremity resulting in complete disability.

When the extremity must be sacrificed for any of these reasons, the choice of the level of amputation depends on the character of the lesion and the blood supply to the individual case. If the lesion is limited to a digit, the blood supply is good, and no infection exists proximal to the base, the digit alone can be amputated, preferably through the head of the metatarsal.

If infection or gangrene of the foot (particularly on the dorsum) has become resistant to local treatment or endangers life by extension proximally, amputation of the leg becomes necessary. In rare instances with exceptionally good blood supply and no gangrene an amputation through the foot or ankle is justified, but ordinarily it leads to the necessity for reamputation if done so low in a foot with obliterative arterial disease.

Amputation above the knee probably is the safest procedure when blood supply is poor although recently excellent results are obtained in skillful and expen-

— of tension due to — and closure of the stump by means of a small drain

Refrigeration of an infected gangrenous extremity is advantageous for preservation of the leg if amputation must be delayed for any reason for reduction in toxemia and for relief of pain. It is of no particular value in local treatment or as anesthesia and it may result in further impairment of blood supply at the amputation level. Its chief indications and effects are the same as those for amputation and removal of the leg under spinal or safe general anesthesia ordinarily is preferable.

The prognosis of trophic lesions of the feet is excellent as a rule even though the bones are involved. With débridement and protection from trauma and infection superficial lesions heal in a week or two. Deep lesions with adherent sloughs may take several weeks or even months to heal and aseptic necrosis of the bones of the foot invariably heals in time if not injured or infected. Gentle dissection and separation of the necrotic skin forming the adherent sloughs in the deep skin lesions and the healing of these persistent lesions. Dissection must be accomplished however without trauma to surrounding tissues or introduction of infection.

Infectious Diseases. The management of diabetes complicated by tuberculosis varies from that ordinarily prescribed only in so far as higher diets and more exact adjustment of sugar metabolism are desirable.

Body weight and nitrogen balance are more difficult to maintain because of the increased metabolism so frequently accompanying the infection. Instead of the usual 25 to 30 calories per kilogram per day 40 or 50 may be required for normal nutrition in adults and correspondingly more in children. The increased caloric requirement generally runs in direct proportion to the degree of fever and toxemia. The protein

intake should be 1.5 to 2 gm per kilogram per day for adults.

Treatment of all urinary tract infections in diabetes consists of (1) elimination of glycosuria continuously (2) avoiding trauma and contamination whenever possible (3) the use of measures appropriate for the treatment of urinary infection in anyone without diabetes. The first objective involves the intelligent application of ordinary or emergency methods of diet and insulin control as indicated by the character of the infection. The second demands extreme caution on the part of the urologist, surgeon, gynecologist or internist in the use of instrumentation of the urinary tract. The use of appropriate urinary antiseptics with in-

— of dia- betes — simply means that any method of treatment appropriate for infections of the urinary tract in nondiabetic patients may be applied as well in diabetes provided that good

may be

Sulfonamides are a sugar metabolism in nontoxic dosage. Acid therapy must be used with caution whenever ketogenic or uremic acidosis threatens or has existed recently but are perfectly safe if the alkali reserve is normal and ketogenic acidosis is prevented postoperatively. If diabetes is kept under good control endoscopy and surgical manipulations are fully as safe and effective as in patients without diabetes.

It is important to search for fungous infection between the toes and other skin folds and eliminate it before it leads to pyogenic infection. The usual methods of treatment are effective except that strong fungicides which may be irritating in themselves should be avoided as all forms of chemical, thermal and mechanical trauma in feet which have

vulvar — and — out lo- — marked dermatitis the lesions persist even after de-sugarization, and further local treatment

required. For the acute stages warm compresses of 0.5 per cent borax in water (1 teaspoon to 1 qt. of water) are effective. Hot sitz baths in borax solution may also be used. When acute inflammation subsides daily painting of the lesions with 1 or 2 per cent tincture of gentian violet usually clears the residue of monilial infection without further difficulty. The best preventive treatment is avoidance of glycosuria.

Lipoid and Allergic Disorders. Xanthomas undergo involution and disappear leaving pigmented scars when blood fats are reduced to normal by good control of glucose metabolism with insulin. Low fat diets probably aid in the restoration of blood fat levels to normal but undoubtedly adequate glucose utilization is more important. These lesions now are seen much more rarely because of the prevention of extreme hyperlipemia owing to better control of sugar metabolism.

Necrobiosis lipoidica diabetorum is uninfluenced by any local treatment and control of the diabetes has no effect on it. The lesions occasionally recede spontaneously leaving atrophic skin. Ulceration may occur

Prevention of insulin atrophy is possible by systematic rotation of injection sites so that no area of the skin receives insulin more often than once every 2 or 3 weeks. This is unnecessary in patients who are free from any tendency toward atrophy but in those who are susceptible it is the only known method of preventing marked disfigurement. When atrophy has already occurred insulin may be injected into the abdominal wall where cosmetic defects are unimportant.

Lipomas due to repeated injections of insulin into the same location should be prevented like atrophy by systematic rotation of the injection site and by frequent examination especially in children to be sure that this is being done. Once they form they are relatively permanent.

When generalized urticaria is linked unmistakably with any given insulin preparation substitution of another form or brand of insulin may eliminate the difficulty. If all forms of insulin cause difficulty desensitization can be accomplished within a day or so by injections of gradually increasing doses every half hour or hour according to the dosage schedule shown in Table VII.

TABLE VII*
DESENSITIZATION TO INSULIN

Dilution of Insulin †	Subcutaneous Dosage at One half to One hour Intervals			
1 100 000	0.1 cc	increasing to 1 cc	by 0.1 cc	additions
1 10 000	"	"	"	"
1 1 000	"	"	"	"
1 100	"	"	"	"
1 10 ‡	"	"	"	"
Undiluted ‡	"	"	"	"

* See footnote Table II

† In normal saline

‡ Increase interval between injections sufficiently to avoid hypoglycemia

Local allergic reactions due to insulin often fail to occur if the insulin is injected into the loose areolar tissue under the fatty panniculus instead of into the fat as the ordinary injection is made. For this purpose a longer needle ($\frac{3}{4}$ to 1 in.) is necessary and the injection must be made into the side of the fold of the skin under the fingers which lift it. The fold between the fingers of one hand and the thumb of another may stop

the lesions. In the order of their tendency to cause reactions of this type the various insulin preparations may be listed as follows: protamine zinc insulin, protamine insulin mixtures, globin insulin, regular insulin, solution of zinc insulin crystals.

If neither of these two devices stops the formation of the wheals and desensitization as described above is impracticable persistence in the use of the offending insulin preparation usually accomplishes desensitization.

zation automatically in the course of a few weeks. The tendency almost always disappears in the course of time even with the most sensitive individuals.

Pregnancy. Control of the diabetes and nutritional status of the pregnant diabetic woman involves (1) increases in the diet as indicated by the body weight (allowing for edema and polyhydramnion) especially during the latter half of pregnancy (2) elimination of abnormal hyperglycemia and glycosuria in so far as possible without insulin shock and unendurable inconveniences (3) respect for the renal type of glycosuria which commonly occurs near term.

The experience of White indicates that hormonal replacement therapy should be prescribed in addition. Stilbestrol and progesterone are both given in daily doses of 5 mg. of each up to the 20th week of pregnancy. Thereafter the dosage of each is increased by 5 mg. every fourth week until parturition when a total dosage of 30 to 50 mg. is given daily. During infections with fever the dosage should be doubled. In a large group of patients so treated the fetal survival rate has increased from about 50 to 90 per cent and the toxemia rate has fallen from about 50 to 5 per cent. More recently the use of stilbestrol alone in dos-

The two most important obstetrical problems demand decisions regarding the optimal time and the best method of delivery. The size of the fetus and its tendency to premature death in utero loom large in influencing both of these decisions.

The size of the baby should not be judged by the size of the abdomen or the weight of the patient because of the prevalence of polyhydramnion under these conditions. Radiologic as well as palpatory evidence should be relied on. If the infant is judged to be large it is often the case premature delivery is indicated. White advises delivery in the 37th week of gestation unless the baby is determined to be unusually large in which case it is accomplished even earlier. Because of the high incidence of fetal death in utero this policy seems wise.

The route of delivery should be deter-

mined by the size of the fetus previous obstetrical experiences in the same patient, the pelvic measurements, the position of the fetus and the degree of effacement of the cervix at the time delivery is considered to be opportune. In a high percentage of patients the net result of weighing this evidence determines that abdominal delivery by cesarean section is the method of choice. Two thirds of the patients in White's series have been delivered by section under spinal anesthesia and without preliminary medication. If normal labor occurs small amounts of barbiturate and scopolamine are used and the third stage is conducted under spinal or gas oxygen anesthesia. The diabetes must be managed by the same emergency methods required for any other type of surgery with generous amounts of carbohydrate particularly if a long difficult labor ensues.

The treatment of neonatal complications is suggested by their character. Sedation during surgical delivery must be used sparingly and oxygen freely. Prompt postural and mechanical clearing of the upper air passages seems to be far more important than is usually the case after delivery. Restriction of fluids after delivery is indicated and weight loss welcomed if the infant is edematous. Glucose subcutaneously or orally should always be given and the response observed if abnormal lethargy, cyanosis or convulsive states appear. The response to glucose is more reliable as an indication of hypoglycemia than the blood sugar level because the latter normally varies from 40 to 70 mg. per 100 cc. of blood soon after birth. If dramatic improvement occurs with glucose it must be repeated at frequent intervals either by mouth by gavage or parenterally until symptoms stop recurring between feedings. Finally atelectasis must always be suspected if cyanosis is present even though the air passages are clear. In addition to oxygen a mixture of 5 per cent carbon dioxide in oxygen for a few minutes out of each hour may be of lifesaving importance.

ARTHUR R. COLWELL

REFERENCES

- Atwater W. O. and Bryant A. P. *Chemical Composition of American Food Materials*. Washington

required. For the acute stages warm compresses of 0.5 per cent borax in water (1 teaspoon to 1 qt of water) are effective. Hot sitz baths in borax solution may also be used. When acute inflammation subsides daily painting of the lesions with 1 or 2 per cent tincture of gentian violet usually clears the residue of monilial infection without further difficulty. The best preventive treatment is avoidance of glycosuria.

Lipoid and Allergic Disorders. Xanthomas undergo involution and disappear leaving pigmented scars when blood fats are reduced to normal by good control of glucose metabolism with insulin. Low fat diets probably aid in the restoration of blood fat levels to normal but undoubtedly adequate glucose utilization is more important. These lesions now are seen much more rarely because of the prevention of extreme hyperlipemia owing to better control of sugar metabolism.

Necrobiosis lipoidica diabetorum is uninfluenced by any local treatment and control of the diabetes has no effect on it. The lesions occasionally recede spontaneously leaving atrophic skin. Ulceration may occur.

Prevention of insulin atrophy is possible by systematic rotation of injection sites so that no area of the skin receives insulin more often than once every 2 or 3 weeks. This is unnecessary in patients who are free from any tendency toward atrophy but in those who are susceptible it is the only known method of preventing marked disfigurement. When atrophy has already occurred insulin may be injected into the abdominal wall, where cosmetic defects are unimportant.

Lipomas due to repeated injections of insulin into the same location should be prevented like atrophy by systematic rotation of the injection site and by frequent examination especially in children to be sure that this is being done. Once they form they are relatively permanent.

When generalized urticaria is linked up mistakenly with any given insulin preparation substitution of another form or brand of insulin may eliminate the difficulty. If all forms of insulin cause difficulty desensitization can be accomplished within a day or so by injections of gradually increasing doses every half-hour or hour according to the dosage schedule shown in Table VII.

TABLE VII*
DESENSITIZATION TO INSULIN

Dilution of Insulin†	Subcutaneous Dosage at One Half to One Hour Intervals				
1 100,000	0.1 cc.	increasing to 1 cc.	by 0.1 cc.	additions	
1 10,000	"	"	"	"	"
1 1,000	"	"	"	"	"
1 100	"	"	"	"	"
1 10†	"	"	"	"	"
Undiluted‡	"	"	"	"	"

* See footnote Table II.

† In normal saline.

‡ Increase interval between injections sufficiently to avoid hypoglycemia.

Local allergic reactions due to insulin often fail to occur if the insulin is injected into the loose areolar tissue under the fatty panniculus instead of into the fat as the ordinary injection is made. For this purpose a longer needle ($\frac{3}{4}$ to 1 in.) is necessary and the injection must be made into the side of the fold of the skin under the fingers which lift it instead of into the crest of the fold between the fingers (Fig. 1). Substitution of another brand or modification of insulin may stop

the lesions. In the order of their tendency to cause reactions of this type the various insulin preparations may be listed as follows: protamine zinc insulin, protamine insulin mixtures, globin insulin, regular insulin, solution of zinc insulin crystals.

If neither of these two devices stops the formation of the wheals and desensitization as described above is impracticable persistence in the use of the offending insulin preparation usually accomplishes desensiti-

zation automatically in the course of a few weeks. The tendency almost always disappears in the course of time, even with the most sensitive individuals.

Pregnancy. Control of the diabetes and nutritional status of the pregnant diabetic woman involves (1) increases in the diet as indicated by the body weight (allowing for edema and polyhydramnion), especially during the latter half of pregnancy, (2) elimination of abnormal hyperglycemia and glycosuria in so far as possible without insulin shock and unendurable inconveniences, (3) respect for the renal type of glycosuria which commonly occurs near term.

The experience of White indicates that hormonal replacement therapy should be prescribed in addition. Stilbestrol and progesterone are both given in daily doses of 5 mg. of each up to the 20th week of pregnancy. Thereafter the dosage of each is increased by 5 mg. every fourth week until parturition, when a total dosage of 30 to 50 mg. is given daily. During infections with fever the dosage should be doubled. In a large group of patients so treated the fetal survival rate has increased from about 50 to 100 per cent, and the toxemia rate has fallen from about 50 to 5 per cent. More recently the use of stilbestrol alone in dos-

ages determined by the size of the fetus, previous obstetrical experiences in the same patient, the pelvic measurements, the position of the fetus, and the degree of effacement of the cervix at the time delivery is considered to be opportune. In a high percentage of patients the net result of weighing this evidence determines that abdominal delivery by cesarean section is the method of choice. Two-thirds of the patients in White's series have been delivered by section, under spinal anesthesia and without preliminary medication. If normal labor occurs, small amounts of barbiturate and scopolamine are used and the third stage is conducted under spinal or gas oxygen anesthesia. The diabetes must be managed by the same emergency methods required for any other type of surgery, with generous amounts of carbohydrate, particularly if a long, difficult labor ensues.

The treatment of neonatal complications is suggested by their character. Sedation during surgical delivery must be used sparingly, and oxygen freely. Prompt postural and mechanical clearing of the upper air passages seems to be far more important than is usually the case after delivery. Restriction of fluids after delivery is indicated and weight loss welcomed if the infant is edematous. Glucose subcutaneously or orally should always be given and the response observed if abnormal lethargy, cyanosis, or convulsive states appear. The response to glucose is more reliable as an indication of hypoglycemia than the blood sugar level because the latter normally varies from 40 to 70 mg. per 100 cc. of blood soon after birth. If dramatic improvement occurs with glucose, it must be repeated at frequent intervals, either by mouth, by gavage, or parenterally, until symptoms stop recurring between feedings. Finally, atelectasis must always be suspected if cyanosis is present, even though the air passages are clear. In addition to oxygen, a mixture of 5 per cent carbon dioxide in oxygen for a few minutes out of each hour may be of lifesaving importance.

ARTHUR H. COLWELL

REFERENCES

- Atwater W. O., and Bryant, A. P. *Chemical Composition of American Food Materials*. Washing-

The two most important obstetrical problems demand decisions regarding the optimal time and the best method of delivery. The size of the fetus and its tendency to premature death in utero loom large in influencing both of these decisions.

The size of the baby should not be judged by the size of the abdomen or the weight of the patient because of the prevalence of polyhydramnion under these conditions. Radiologic as well as palpatory evidence should be relied on. If the infant is judged to be large, as is often the case, premature delivery is indicated. White advises delivery in the 37th week of gestation, unless the baby is determined to be unusually large, in which case it is accomplished even earlier. Because of the high incidence of fetal death in utero this policy seems wise.

The route of delivery should be deter-

- ton D C Office of Experimental Stations 1906
Bull no 28 (revised)
- Bang H O Some Investigations on the Absorption Mechanism of Protamine Insulin *Acta pharmacol et toxicol* 2 79 1946
- Bang H O Enzymatic Breakdown of Protamine Insulin *Acta pharmacol et toxicol* 2 89 1946
- Banting F G and Best C H Internal Secretion of Pancreas *J Lab & Clin Med* 7 251 1922
- Barborka C J Fatty Atrophy from Injections of Insulin *JAMA* 87 1646 1926
- Bauman L Clinical Experience with Globin Insulin *Am J M Sc* 198 475 1939
- Beardwood J T Jr and Rouse G P Jr Diabetic Acidosis Study of 220 Consecutive Cases *JAMA* 117 1701 1941
- Bellows J G The Crystalline Lens in Diabetes Mellitus *Arch Ophthalmol* 32 498 1944
- Blatherwick N H Larson H W and Sawyer S D Metabolism of d Mannoheptulose Excretion of Sugar after Eating Avocado *J Biol Chem* 133 643 1940
- Bowen B D and Kutzman N Urinary Tract in Diabetic Women Its Contribution to Incidence of Hypertension *Ann Int Med* 17 427 1942
- Bridges M A and Matice M R *Food and Beverage Analysis* Ed 2 Philadelphia Lea & Febiger 1942
- Castellani A Mycological Methods in Identification of Various Sugars and Other Carbon Compounds *J State Med* 39 621 1931
- Chatfield C and Adams G *Proximate Composition of American Food Materials* Washington D C U S Dept Agriculture Circular no 549
- Colwell A R *Diabetes Mellitus in General Practice* Chicago Year Book Publishers 1947
- Colwell A R Effective Insulin Timing in Diabetes Mellitus *M Clin North America* 31 397 1947
- Colwell A R Protamine Insulin Mixtures in Treatment of Diabetes Mellitus *New York State J Med* 47 1103 1947
- Colwell A R Nature and Time Action of Modifications of Protamine Zinc Insulin *Arch Int Med* 74 831 1944
- Colwell A R Observed Course of Diabetes Mellitus and Inferences Concerning Its Origin and Progress *Arch Int Med* 70 523 1942
- Colwell A R and Izzo J L Protamine Zinc Insulin Modified for Accelerated Action *JAMA* 122 1231 1943
- Colwell A R Izzo J L and Stryker W A Intermediate Action of Mixtures of Soluble Insulin and Protamine Zinc Insulin *Arch Int Med* 69 931 1942
- Depisch F Über lokale Lipodystrophie bei langer Zeit mit insulinbehandelten Fällen von Diabetes *Klin Wchnschr* 5 1905 1926
- Du Bois E F and Chambers W H *Handbook of Nutrition Calories in Medical Practice* *JAMA* 119 1183 1942
- Duncan G G and Barnes C A Action of Globin Insulin Compared with That of Crystalline Unmodified and Protamine Zinc Insulin *Am J M Sc* 202 553 1946
- Eastman N J Diabetes Mellitus and Pregnancy A Review *Obst & Gynec Surv* 1 1946
- Exton W G and Rose A H Diabetes as Life Insurance Selection Problem *Proc A Life Insur M Dir America* (1931) 18 252 1939
- Goldner M G Insulin Lipohypertrophy *J Clin Endocrinol* 3 469 1943
- Jensen H F *Insulin Its Chemistry and Physiology* New York The Commonwealth Fund, 1933
- Joslin M P et al Diabetic Coma *JAMA* 119 1160 1942
- Joslin E P et al Diabetic Coma *Arch Int Med* 59 175 1937
- Joslin E P et al Protamine Insulin *New England J Med* 214 1079 1936
- Kimmelstiel P and Wilson C Intercapillary Lesions in Glomeruli of the Kidney *Am J Path* 12 83 1936
- Kussmaul A Zur Lehre vom Diabetes mellitus Ueber eine eigenthümliche Todesart bei Diabeteschen ueber Acetonaemie Glycerin Behandlung des Diabetes und Einspritzungen von Diastase ins Blut bei dieser Krankheit *Deutsches Arch f klin Med* 141 1 1874
- Larpy T C Eitzen O and Dutra F R Intercapillary Glomerulosclerosis *Arch Int Med* 74 854 1944
- Lawrence R D Symptomless Glycosurias Differentiation by Sugar Tolerance Tests *M Clin North America* 31 289 1947
- Lawrence R D Mayer A and Nevin S Pathological Changes in Brain in Fatal Hypoglycemia *Quart J Med* 11 181 1942
- Marble A The Diagnosis of the Less Common Mellituras *M Clin North America* 31 313 194
- Marble A and Smith R M Atrophy of Subcutaneous Fat Following Injections of Insulin *Proc Am Diabetes A* 2 171 1942
- Matthews M W Magath T B and Berkson J One Hour Two Dose Dextrose Tolerance Test (Exton Rose Procedure) Diagnostic Significance *JAMA* 113 1531 1939
- McKutnick L S Recent Advances in Management of Gangrene and Infections in Patients with Diabetes Mellitus *Am J Digest Dis* 13 14 1946
- Newburgh L H and Conn J W New Interpretation of Hyperglycemia in Obese Middle-aged Persons *JAMA* 112 7 1939
- OB
Y
Pec
M Clin North America 31 343 1947
- Peck F B Action of Insulins *Proc Am Diabetes A* 2 67 1942
- Peck F B and Schechter J S Newer Insulin Mixtures Follow up Study *Proc Am Diabetes A* 4 5 1945
- Remer L Searle D S and Ladg H H On Hyperglycemic Activity of Globin Insulin *J Pharmacol & Exper Therap* 67 330 1939
- Ricketts H T Does Hyperglycemia Harm the Diabetic Patient? *M Clin North America* 31 267 1947

- [illegible]

HEMOCHROMATOSIS

There is no specific treatment for hemochromatosis. Mallory's theory that it is due to chronic copper intoxication suggests that a search should be made for this metal in the patient's intake.

The diabetes so frequently associated

should be managed by orthodox methods. Marked improvement can be expected temporarily with good nutrition and control of abnormal hyperglycemia and glycosuria. Insulin resistance is seen not infrequently possibly as a result of liver damage. Massive maintenance doses of insulin then may be required. They should be employed without hesitation if the glycosuria fails to respond to ordinary dosage.

Diets containing at least 200 gm carbohydrate and 100 gm protein daily help to prevent and correct hepatic damage. Choline or methionine should be given in dosage of 3 to 6 gm daily. Gratifying results in male patients with hemochromatosis have been reported after therapy with testosterone 25 mg three to five times weekly should be administered by intramuscular injection for a trial period of several weeks and continued at a somewhat lower rate if encouraging signs are evident. Ascites may demand paracentesis.

Usually however, unless improvement can be obtained by correction of the diabetic state the results of treatment are discouraging in proved hemochromatosis.

ARTHUR R. COLWELL

REFERENCES

- Bailey C C Hemochromatosis in *The Treatment of Diabetes Mellitus* Philadelphia Lea & Febiger 1946
- Beardwood J T Jr and Rouse G P Jr Hemo-
chromatosis in *Diabetes Mellitus* New York 1946
- Allen et al W R Hemochromatosis in *Lies Practice of Medicine* Hagerstown Md W F Prior Co Inc 1942 Vol 9 p 59
- Mallory F B and Parker F Jr Microchemical Demonstration of Copper in Pigment Cirrhosis *Am J Path* 7:365 1931
- Sheldon J H Hemochromatosis London H Milford 1935

HYPERINSULINISM

Hyperinsulinism may be characterized as a definite clinical entity while a spontaneous (functional) hypoglycemia may result from

Whatever the origin of a hypoglycemia the symptoms for a given blood sugar level of some duration are essentially the same. They are a result of the effect of an inadequate plasma and interstitial fluid glucose level on nervous tissue. In mild attacks sweating flushing palpitation etc perhaps all the result of a hypoglycemic epinephrine discharge predominate. In severe attacks thick speech muscle spasm etc are prominent and eventually result in coma and death.

Hyperinsulinism in the true sense may occur as a compensatory secretory reaction or as a result of a temporary hyperplasia of the islands of Langerhans in infants born to mothers with uncontrolled diabetes (i.e. with chronic hyperglycemia). This functional hyperinsulinism is becoming increasingly rare with the more adequate control of diabetics during pregnancy. The chief problem is the rapid recognition of the ailment at birth or of its possibility prior to delivery. If normal feeding plus glucose therapy is adequate during the first 4 days of life the danger of a fatal outcome from this temporary type of hyperinsulinism is largely removed.

The clinical complex generally thought of as hyperinsulinism and which is due to hyperfunction hyperplasia or tumors of the islands of Langerhans is of a chronic nature. It is a rare disease with a silent onset. In the first attack the hypoglycemia may lead to loss of consciousness but milder episodes usually initiate the ailment. Diagnosis may not be easy and is essential for proper therapy. The fasting blood sugar should be below 60 mg per 100 cc. Symptoms of a hypoglycemia accompanied by a blood sugar level below 40 mg per 100 cc are evidence for hyperinsulinism. "Hypoglycemic attacks brought on by long periods without food (omission of breakfast) and by moderate exercise point in the same direction. Immediate relief from hypoglycemic symptoms by the intravenous injection of glucose solution is an important test. A routine glucose tolerance test may complete the diagnosis but Conn has stressed the importance of a glucose tolerance test carried out under standard conditions. Duncan gives 350 gm carbohydrate 125 gm protein per kilogram of body weight and fat to a total of 35 calories per kilogram of

body weight per day for 3 days prior to the glucose tolerance test. Under these conditions a patient with hyperinsulinism has a subnormal fasting blood sugar level a test peak not over 120 mg per 100 cc and a return to subnormal values within 3 hours which is then maintained for several hours. Some of the conditions in which different results are obtained are outlined under functional hypoglycemia. As another diagnostic point Duncan adds the remarkable rate at which intravenously administered glucose is disposed of in hyperinsulinism.

hydrate in much the same way as an overdose of insulin. If the patient is in coma, intravenous administration of a glucose solution is necessary. Epinephrine is no more useful than for an overdose of insulin in the diabetic. Although a special diet is effective in many cases of functional hypoglycemia, it is futile in hyperinsulinism due to islet cell tumors. Preparation for the operation entails the giving of large amounts of protein and slowly absorbed carbohydrate (bread cereal fruits) every 3 or 4 hours for at least

noma of the islands of Langerhans since these tumors easily become malignant an operation should never be delayed when it is indicated. When neither an adenoma nor a carcinomatous nodule is located at the time of surgery partial resection of the pancreas has been advocated by Wilder. This may lead to the development of diabetes which may be controlled with diet and insulin. The intravenous administration of 10 per cent glucose solution is useful during surgery and insulin may be needed in small amounts for a few days postoperatively. It is generally unnecessary. No drugs of any kind are efficacious in treating hyperinsulinism.

Functional Hypoglycemia Functional hypoglycemia differs from hyperinsulinism in that there is no absolute overproduction of insulin concerned in the pathogenesis of the lowered blood sugar level and with the exception of one group of cases a high carbohydrate intake is desirable therapy. There are many causes of functional hypoglycemia.

and the treatment, if any, varies with the origin

Relative hyperinsulinism is a common cause of functional hypoglycemia. Insulin secretion is not abnormal but is sufficiently high for the existing conditions to be in excess of opposing factors and thus cause hypoglycemia.

When intravenous glucose therapy which has been continued for some time is suddenly stopped, particularly in infants or children, a transient physiologic hyperinsulinism may exist for a time and hypoglycemia result. The same effect may be observed in undernourished subjects or after short periods of fasting as postoperatively when glucose solutions are used for restoration of the fluid balance. The hypoglycemia following the sudden discontinuance of glucose therapy has little clinical interest and is easily prevented or controlled by a slower withdrawal of the glucose therapy.

A number of endocrine diseases may lead to severe hyperglycemia based on relative hyperinsulinism. A rare but typical example of this state is Simmonds' disease or hypophyseal cachexia which occurs with atrophy of the anterior pituitary gland. Tumors of the anterior lobe may have a similar effect. In either case the hypoglycemia is a secondary feature of the disease and fails to confuse the clinical diagnosis or govern the therapy.

Addison's disease or adrenal insufficiency may cause a hypoglycemia much as does anterior pituitary deficiency, by removing a normal insulin opposing secretion. The other clinical features make it possible to classify such patients properly.

Hypothyroidism especially following thyroidectomy for Graves' disease may occasionally give rise to the clinical symptoms of hypoglycemia. Other symptoms should make it possible to reach the proper diagnosis and thyroid therapy rapidly corrects the hypoglycemia.

A lack of carbohydrate food due to starvation or food loss by vomiting or diarrhea is frequently the cause of mild clinical evidences of hypoglycemia. Except for the immediate use of glucose to combat the acute symptoms a consideration of the treatment

during lactation. In both cases the possibility of hypoglycemia should be kept in mind and if symptoms occur, an increase in the number of meals per day, with or without an increased total food intake, is indicated.

Liver disease must be severe to be the cause but is not infrequently the origin of a mild hypoglycemia. The liver normally is a most important factor in the blood sugar regulation, removing sugar to form glycogen during hyperglycemia and forming sugar from carbohydrate or protein sources when a low blood sugar concentration indicates that it is needed. If sufficient liver tissue is destroyed or physiologically inactivated, the hepatic blood sugar regulating mechanism may be upset sufficiently to give rise to a chronic hypoglycemia. Acute yellow atrophy, grossly disseminated hepatic or metastatic tumors or other extensive diseases of the liver cause an obvious hypoglycemia. Ascending cholangitis, infections, hepatitis, and cirrhosis of the liver are the more common offenders. Diagnosis may at times be difficult. As in hyperinsulinism acute symptoms are controlled by glucose injections, fasting blood sugar levels are subnormal, and glucose tolerance tests return to hypoglycemic levels. The real distinction is that unlike hyperinsulinism, patients with liver disease and hypoglycemia have glucose tolerance tests which are diabetic in nature, rising to high levels for several hours after the ingestion of the glucose, showing an unpaired ability to remove glucose from the blood stream.

The treatment of the hypoglycemia of liver disease is unlike that for hyperinsulinism in that a low fat intake is essential. The fat intake can have no direct influence upon the hypoglycemia and if at a normal level or higher, can be deleterious to the course of the liver ailment. A liberal protein intake

supplied indefinitely by carbohydrate, but to protect the liver from further damage. The daily carbohydrate intake may be as high as is necessary to prevent symptoms of hypoglycemia. If the ailment necessitates an operative procedure such as cholecystectomy, preoperative treatment also includes a high carbohydrate intake (to 500 gm per day)

and as much protein as the patient can take

Diseases of the nervous system occasionally give rise to hypoglycemia. Intracranial injuries, subdural hemorrhage, and general paresis are the most common examples. The low blood sugar level rarely confuses the diagnosis and treatment of this disturbance as such is never necessary.

Functional disturbances of the sympathetic nervous system provide the largest group of patients presumed to have chronic hypoglycemia. They comprise those individuals with neurocirculatory asthenia, vagotonia, and various neuroses. The bulk of them suffer from mild "hypoglycemic" symptoms but have no hypoglycemia. Carbohydrate or other food fails to relieve their symptoms (weakness, fatigue, palpitation, etc.), and they feel faint without reference to meals. Neither fasting nor physical exercise provokes their symptoms and fasting blood sugar values are not abnormal.

Some patients in the neuroses group do suffer from mild degrees of hypoglycemia and have flat glucose tolerance curves. Conn has designated the hypoglycemia of neurosis as a functional hyperinsulinism but it would seem more reasonable to assume that it is associated with the vagotonia or other disturbances of the sympathetic nervous system. In any case a special diet gives relief to practically all of these patients. Conn suggests that for the average adult the carbohydrate content should not exceed 150 gm per day and is best provided in a nonsugar and slowly absorbable form (e.g., bread, cereals, fruit, etc.). High protein (120 to 140 gm per day) and fat contents (170 to 200 gm) are recommended. The carbohydrate content is kept low because glucose stimulates sugar storage and contributes to the hypoglycemia. The high protein content is based on the slow metabolism and steady release of glucose formers by this element of the diet. Waters first reported on the use of a high fat diet which Wilder had already used at the suggestion of his dietitian. The rationale of the high fat content may be a reduction in the emptying time of the stomach with a consequent slower release to the circulation of the carbohydrate in the diet.

Of even more importance than the composition of the diet used in combating neurotic hypoglycemia is the quantity of food

The total diet should have a high caloric value, at least 30 to 40 calories per kilogram of body weight. Any increase in body weight if the patient is underweight and a moderate increase if already of normal weight may contribute to a marked amelioration of symptoms. The diet can be divided into three meals and three nourishments in midmorning, midafternoon, and on retiring.

Physical exercise which lowers the blood sugar should be restricted until the hypoglycemia has been controlled. If exercise cannot be avoided, extra carbohydrate food should be taken a short time beforehand. There are no drugs which are directly useful in the treatment of patients with hypoglycemia. Epinephrine is no exception for its effect is of short duration and dependent on the carbohydrate stores in the patient's liver.

EATON M. MACKEY

REFERENCES

- Conn, J. W. Spontaneous Hypoglycemia: Importance of Etiology in Determining Treatment. *JAMA* 115:1669, 1940.
- Conn, J. W. Advantage of High Protein Diet in Treatment of Spontaneous Hypoglycemia. Preliminary Report. *J. Clin. Investigation*, 13:973, 1936.
- Duncan, G. G. (Editor). *Diseases of Metabolism, Detailed Methods of Diagnosis and Treatment. A Text for Practitioners*. Philadelphia: W. B. Saunders Company, 1947.
- Hartmann, A. F., and Jaudon, J. C. Hypoglycemia. *J. Pediatr.* 11:1, 1937.
- Waters, W. C., Jr. Spontaneous Hypoglycemia: Role of Diet in Etiology and Treatment. *South M. J.* 24:243, 1931.
- Whipple, A. O. The Surgical Therapy of Hyperinsulinism. *J. Internat. de Chirurgie* 3:237, 1938.
- Wilder, R. M. *Clinical Diabetes Mellitus and Hyperinsulinism*. Philadelphia: W. B. Saunders Company, 1940.

OBESITY

Whatever the underlying cause, obesity in the last analysis is solely a question of a disturbance in the normal relation of the appetite to the energy expenditure. The obese patient eats too much. The adipose tissue is the normal depository for fat and in the obese this fat deposition is excessive. The extra fat in the adipose tissue may be unusual in its distribution but in most cases it follows normal variations.

Etiology as a Basis of Therapy. Why do

fat people eat too much? This remains a question about which we must speculate. An attractive hypothesis concerns a possible difference in the lipophilic activity (avidity for fat deposition and retention) of the adipose tissue of obese individuals. At the present there is no evidence for this theory although the lipophilic quality of adipose tissue from different parts of the body differs markedly and this characteristic is retained on transplantation of these regional tissues. It is easy to visualize similar variations of a hereditary or constitutional nature which could lead to obesity. Granting that heredity is an important factor in body build, Newburgh denies that it determines the presence of obesity.

The evidence for endocrine factors as causes of obesity is not at all convincing at the present time. There are suggestions that the pituitary, adrenals, pancreas and gonads may influence the deposition of fat but Cushing's disease is almost the only example of true endocrine obesity. There is no evidence which would warrant the use of endocrine preparations in the treatment of obesity.

Better food absorption or more efficiency in energy metabolism have both been used as explanations of the fat patient's plight. No convincing evidence in support of these conceptions has ever been brought forward.

For the present at least we are limited to the conception of an abnormal appetite as the cause of obesity. Like many important self-regulatory functions, the appetite appears to be centered in the hypothalamus. The cerebral cortex exerts a modifying influence on the functions of the lower nervous centers and appetite is no exception. This brings up the question of psychologic factors in the origin of obesity. This subject has been well studied in children and such factors are obvious to anyone who treats the obese at any age. In spite of this fact, psychiatric treatment has aided us little in weight reduction. Diet accompanied by accessory measures is the basis of therapy.

Objectionable Therapy. Endocrine products with the exception of thyroid preparations when they are used for their calorigenic effect are not indicated as aids to weight loss in obesity.

Ipecac, emetine, belladonna preparations, digitalis, dinitrophenol, saline cathartics

etc. have all had their advocates but are contraindicated in the weight reduction program.

Heat cabinet baths to reduce body weight are ill advised. Water restriction as well as administration of diuretics to promote water loss are also undesirable.

Exercise has often been recommended as a means of increasing the energy expenditure. Unfortunately it usually increases the

and subcutaneous tissues.

Accessory Therapy. The energy expenditure may be increased by thyroid administration, the drug acting as a pharmacologic calorigenic agent and not as an endocrine replacement. It causes body protein loss and has many undesirable side effects. Most workers oppose its use and there are definite objections to its administration to obese children. It is well to remember that thyroid medication can replace the secretion of thyroglobulin by the normal thyroid gland and when the drug is discontinued the basal metabolic rate may fall far below normal. Obesity does not stem from hypothyroidism and patients with this disturbance are rarely obese. If one feels that thyroid medication must be used, doses of 1 to 3 grains of desiccated thyroid USP per day are suitable.

significant degree of cardiovascular disease is allowed such medication.

An extensive literature has accumulated on the use of sympathomimetic amines in the treatment of obesity. Desoxyephedrine and propadrine hydrochloride have had their proponents but are now in the discard. Amphetamine (benzedrine sulfate) has given good results for 13 years and more recently the dextrorotatory optical isomer (dextedrine sulfate) which appears to have fewer undesirable side effects has come into wide use. The dosage is 5 to 30 mg. daily (usually 10 to 20 mg. of dextedrine sulfate) divided into at least two and sometimes three doses. The drugs are never given after late afternoon for they may cause sleeplessness.

Some patients are unable to take the amphetamine preparations because of undesirable excitatory effects. These drugs may cause transient and minor increases in the blood pressure and basal metabolic rate but these effects are rarely troublesome and apparently unrelated to their effect in obesity. Various explanations of the mechanism of amphetamine action in obesity control have been advanced but it is now accepted to be of cerebral origin. It has some effect upon the appetite of the normal subject but is much more efficacious in the person who obtains excessive satisfaction from eating.

There are some patients in whom amphetamine appears to reduce the appetite without any attention to the diet. These people are few in number and the drug is most useful as an adjunct to the low calorie diet.

Effectiveness after prolonged use but following a rest period of several weeks its efficacy may be restored. In any case, the use of amphetamine is a secondary weapon in weight reduction. The low calorie diet is far more important than any form of drug therapy in the management of obesity.

Diet Therapy. Weight can always be reduced if the patient will adhere to a restricted diet. The patient should desire to lose weight and his physician must believe in the therapy used. It may be necessary to stress the health hazards and social objections to overweight. Unless a person has become obese because of a true neurosis, the usual explanations and discussions with a patient will suffice to cause him to undertake a strict reduction regimen.

Regular visits to the physician are essential. They serve to maintain the patient's morale, as a check on his adherence to the regimen and afford an opportunity to answer questions which may arise. An example is the depressing circumstance in occasional cases of water retention so that for some days or weeks the loss of body fat is not evident in daily or weekly weighing. It is wise to explain this possibility in advance.

Excluding the obese patient who resembles the uncontrollable chronic alcoholic,

the difficulty of most obese patients in following a dietary regime is in breaking long established eating habits. This is particularly true during the first 4 to 6 weeks of dieting and the control of the hunger sensation is most important during this period. In a popular proprietary preparation small quan-

the appetite. Another proprietary remedy includes vitamins and minerals but it is not effective in reducing the appetite. Bulk-

questionable answer to hunger control. However, reducing diets tend to result in mild constipation and the all around effect of these bulking agents is generally good. Two or 3 glasses of water satisfy hunger pangs for a short time and most patients may use black coffee or plain tea if they prefer.

The food ingredient with the highest

some promise

A reasonably well balanced diet is desirable for weight reduction. With the extremely low calorie levels (less than 1000 calories) it should be accurately weighed. For less drastic regimes a diet made up of approximate portions will suffice. The greatest success in treating obesity has been achieved when the calories are sharply limited even to 450 calories per day. This is difficult for most patients and 600 calories or even 900 calories is to be preferred for the minimum. Protein is provided in the amount of not less than 1 gm. per kilogram per day for with this quantity nitrogen balance is maintained. Not more than 20 per cent of the calories are fat, in order to have carbohydrate for bulk and to prevent ketosis. The carbohydrate is best supplied by low carbohydrate fruits and vegetables because of their bulk. With the lower calorie diets non-therapeutic doses of the fat soluble vitamins are useful food supplements. Two good multiple vitamin capsules per day may be used. If milk and its products are excluded to obtain a very low calorie or

intake, 1 to 2 gm of calcium phosphate each day is recommended

The stringency of the diet used will depend upon the age and general condition of the patient. Children should not have their calories severely restricted. Most reducing diets are ketogenic and the fewer the calories the greater their ketogenic action. Although ketosis embarrasses obese subjects less than others, the development of a severe ketosis is undesirable in the child and in the female of any age, both of whom are rather susceptible to this condition.

The disadvantages of obesity have been well analyzed but there are a few patients whose weight must be reduced slowly and with extreme caution. These include aged subjects and patients with cirrhosis of the liver, peptic ulcer and rarely chronic ulcerative colitis, malignancy and active tuberculosis.

Some obese patients will find it impossible to submit to a strict dietary regimen and others will choose to avoid the inconvenience and removal of their eating pleasure. Except for a few whom the psychiatrist may aid if they can afford the time and expense we have nothing to offer these people. They will have to keep their disease.

When an obese patient has had his weight reduced to a normal level the job is not completed. Without supervision the majority of once obese patients will quickly regain their weight. A good basic diet should be prescribed for them and they should check with their physician at not longer than 6 month intervals. In this way it is possible to maintain the results of a hard won battle with occasional periods of mild dieting perhaps 1400 to 1600 calories per day.

800 CALORIE DIET FORM

(Carbohydrate = 67 Protein = 65 Fat = 31)

Breakfast	Amount
10 per cent fruit	1 serving ($\frac{1}{2}$ grape fruit 1 orange or $\frac{1}{2}$ cup)
Egg	1
Toast	1 thin slice
10 00 P.M.	
Skim milk or butter	
1/2 milk	$\frac{1}{2}$ glass

Dinner		
5 or 10 per cent vegetable	2 servings ($\frac{1}{2}$ cup each)	
10 per cent fruit	1 serving (as above)	
Lean meat or cheese	1 medium serving	
3 00 P.M.		
Skim milk or butter		
milk	1 glass	
Supper		
5 per cent vegetable	2 servings ($\frac{1}{2}$ cup each)	
10 per cent fruit	1 serving (as above)	
Lean meat fish or cheese	1 large serving	
8 00 P.M.		
Skim milk or butter		
milk	$\frac{1}{2}$ glass	
Directions		
No butter to be added to vegetables		
Meats may be roasted broiled or stewed		
Use only fresh fruits allowed or fruit canned without sugar		
Vegetables to be prepared without cream cream sauce butter or salad dressing		

1000 CALORIE REDUCTION DIET

(Carbohydrates = 70 Fat = 51 Protein = 65)

Breakfast	Amount
Fruit 10 per cent	1 serving
Egg	1
Toast white or whole wheat	1 thin slice
Butter	$\frac{1}{2}$ teaspoon
Coffee	If desired
Dinner	
5 per cent or 10 per cent vegetables (One may be served as a salad)	2 servings ($\frac{1}{2}$ cup each)
10 per cent or 15 per cent fruit	1 serving
Eggs	2
or	
Meat or cottage cheese	1 small serving
Butter	$\frac{1}{2}$ teaspoon
Milk	1 glass
Supper	
Broth	If desired
5 per cent or 10 per cent vegetables (One may be served as a salad)	2 servings ($\frac{1}{2}$ cup each)
10 per cent or 15 per cent fruit	1 serving
Lean meat fish poultry or cottage cheese	1 large serving
Butter	$\frac{1}{2}$ teaspoon
Milk	1 glass
Water clear broth vinegar tea, and coffee may be used as desired.	

1000 CALORIE DIET (Cont'd)

Meats may be roasted, broiled, or stewed
 Use only fresh fruits allowed or fruit canned with
 out sugar
 Vegetables to be prepared without cream, cream
 sauce, or salad dressings
 May use butter as allowed in diet

1200 CALORIE REDUCTION DIET

(Carbohydrate = 95, Fat = 60, Protein = 70)

<i>Breakfast</i>	<i>Amounts</i>
Fruit, 10 per cent	1 serving
Egg	1
Toast, white or whole wheat	1 thin slice
Butter	$\frac{1}{2}$ teaspoon
Coffee	If desired
<i>Dinner</i>	
5 per cent or 10 per cent vegetables	2 servings ($\frac{1}{2}$ cup each)
(One may be served as a salad)	
10 per cent or 15 per cent fruit	1 serving
Eggs or	2
Meat or cottage cheese	1 small serving
Butter	$\frac{1}{2}$ teaspoon
Bread	1 thin slice
Milk	1 glass

<i>Supper</i>	
Broth	If desired
5 per cent or 10 per cent vegetables	2 servings ($\frac{1}{2}$ cup each)
(One may be served as a salad)	
10 per cent or 15 per cent fruit	1 serving
Lean meat, fish, poul- try, or cottage cheese	1 large serving
Butter	$\frac{1}{2}$ teaspoon
Bread	1 thin slice
Milk	1 glass

Water, clear broth, vinegar, tea, and coffee may be
 used as desired

Meats may be roasted, broiled, or stewed
 Use only fresh fruits allowed or fruit canned without
 sugar

Vegetables to be prepared without cream, cream
 sauce, or salad dressing
 May use butter as allowed in diet

1500 CALORIE REDUCTION DIET

(Carbohydrate = 118, Fat = 84, Protein = 80)

<i>Breakfast</i>	<i>Amounts</i>
Fruit, 10 per cent	1 serving
Egg	1
Toast, white or whole wheat	1 thin slice
Butter	1 teaspoon
or	
Bacon	3 strips
Cream	2 tablespoons
Coffee	If desired

Dinner

5 per cent or 10 per cent vegetables	2 servings ($\frac{1}{2}$ cup each)
(One may be served as a salad)	
10 per cent or 15 per cent fruit	1 serving
Meat	1 medium serving
Butter	1 teaspoon
Bread	1 thin slice
Salad Dressing	1 teaspoon
Milk	1 glass

Supper

Broth	If desired
5 per cent or 10 per cent vegetables	2 servings ($\frac{1}{2}$ cup each)
(One may be served as a salad)	
10 per cent or 15 per cent fruit	1 serving
Potato	1 medium
Lean meat, fish, poul- try, or cottage cheese	1 large serving
Butter	1 teaspoon
Bread	1 thin slice
Milk	1 glass

Water, clear broth, vinegar, tea, and coffee may
 be used as desired

Meats may be roasted, broiled, or stewed
 Use only fresh fruits allowed or fruit canned without
 sugar

Vegetables to be prepared without cream or cream
 sauce

May use butter as allowed in diet

VEGETABLES

<i>5 Per cent</i>	<i>10 Per cent</i>	<i>20 Per cent</i>
Asparagus	Beets	Corn
Artichokes	Carrots	Lima Beans
Beet greens	Kohl-rabi	Baked Beans
Broccoli	Parsley	Parsnips
Brussels sprouts	Peppers	Peas
Cabbage	Pumpkin	Potatoes
Cauliflower	Turnips	Squash Hubbard, Baked
Celery		
Celery cabbage		
Chard		
Cucumbers		
Cucumber pickles		
Dandelion greens		
Endive		
Eggplant		
Lettuce		
Mushrooms		
Okra		
Onions		
Radishes		
Rhubarb		
Sauerkraut		
Spinach		
String beans		
Tomatoes		
Watercress		
Wax beans		
Summer squash		

DISEASES OF METABOLISM

Fruits		
Per cent	15 Per cent	20 Per cent
antaloupe	Apples	Bananas
anberries	Apricots	Figs, fresh
roseberries	Blackberries	Grapes
apefruit	Blueberries	Grape juice
meydw	Cherries	Pomegranate
mons	Loganberries	Plums
mes	Peaches	Prunes, cooked
ranges	Pears	
rawberries	Pineapple	
atermelon	Raspberries	
anned Fruit	Canned Fruit	
thout sugar	without sugar	
11 Per cent	12 15 Per cent	
EATON M. MACKEY		

REFERENCES

- auer, J. Obesity: Its Pathogenesis, Etiology and Treatment. *Arch. Int. Med.*, 67: 968, 1941.
- robeck, J. R. Mechanism of Development of Obesity in Animals with Hypothalamic Lesions. *Physiol. Rev.*, 28: 541, 1948.
- ruck, H. Psychiatric Aspects of Obesity in Children. *Am. J. Psychiat.*, 59: 752, 1943.
- ublin, L. J. Influence of Weight on Certain Causes of Death. *Human Biol.*, 2: 159, 1930.
- larns, S. C. Ivy, A. C., and Searle, L. M. Mechanism of Amphetamine-Induced Loss of Weight. *J. A. M. A.*, 134: 1488, 1947.
- ewburgh, L. H. Obesity, Energy Metabolism. *Physiol. Rev.*, 24: 18, 1944.
- ewburgh, L. H. and Johnston, M. W. Obesity. *M. Clin. North America*, 27: 327, 1943.
- Velis, H. G. Adipose Tissue, A Neglected Subject. *J. A. M. A.*, 114: 2177, 1940.

DIABETES INSIPIDUS

Diabetes insipidus results from an abnormal reduction in the secretion of the antidiuretic factor by the posterior lobe (pars nervosa) of the pituitary gland. In the normal subject this hormone, secreted under the influence of the hypothalamus, insures adequate reabsorption of water by the renal tubules. When the hormone is lacking polyuria ensues and secondary to this uncon-

or the associated nuclei in the hypothalamus. The apparent necessity of a functional anterior pituitary gland and the supposition that it supplies a diuretic factor have been supported by a case of diabetes insipidus due to anterior pituitary overactivity.

If a patient is suffering from diabetes insipidus because of an obvious tumor, tumor developmental abnormality, infection, chromotaxis, or other process in the cephalopituitary area, the treatment of the disease must involve the cause as well as the symptoms. If no underlying lesion is covered, the treatment of which may in improvement or cure, we are limited to an attempt to control the polyuria and

makes this easier or more effective. Restriction is of some value but must be accompanied by sodium chloride restriction, which of itself is far more important. The best results are obtained not alone by exclusion of added salt from the diet (baking soda and baking powder also), but by judicious selection of low salt foods so that the urine contains only a fraction of a gram of sodium chloride per day. But some restriction is better than none, and re-

because of their caloric content. In the case of diet therapy is only palliative, merely serves as an adjunct to therapy with posterior pituitary preparations.

Symptomatic Treatment. Substitution of therapy with active antidiuretic preparation of the posterior pituitary gives good control of the symptoms in almost all patients with diabetes insipidus. They usually have good effects and in most cases may be continued indefinitely. Various preparations and forms are available.

Posterior pituitary injection (solution of posterior pituitary) USP X

USP units per cubic centimeter

"Pituitrin," for surgical use (Parke, Davis & Co.)

meter twice the strength of USP extract

Beta hypophammine NNR — Pitressin™
(Parke Davis & Co) 10 pressor units
per cubic centimeter

Beta hypophammine tannate — Pitressin™
tannate in oil (Parke Davis & Co) 5
pressor units per cubic centimeter

Posterior pituitary powder USP

The original symptomatic treatment of patients suffering with diabetes insipidus made use of subcutaneous or intramuscular injections of aqueous posterior pituitary extract. It is still used generally as "pitressin" in doses of 0.5 to 4 cc daily. A single dose affords relief from symptoms for 4 to 24 hours. In most patients a morning and evening injection is required. "Pitressin" has less of the undesirable stimulating action on the intestine found with the USP or "surgical" extract.

"Pitressin" tannate in oil is the injectable preparation of choice. The injection of 1 cc (containing 5 pressor units) intramuscularly (never intravenously) will control the symptoms of the disease for 24 hours to 3 days. Injections are rarely required more frequently than once a day. The oil injections may be repeated as often as the symptoms require.

Symptoms may be controlled by the intranasal use as a spray or on a swab of the aqueous posterior pituitary extracts. A nasal tampon soaked with 1 cc of extract is placed against the roof of the nasopharynx two or three times daily. The intranasal application method is not regularly effective and it is expensive.

Nasal insufflation of posterior pituitary gland powder is an exceedingly good method of controlling the polyuria and thirst. A dose of about 50 mg may be snuffed from the finger tip or administered with a powder atomizer or blower. The Armour powder inhalator (Armour Laboratories) is specially designed for capsuled powders and posterior pituitary powder is available in this form. The capsule is opened and placed in the chamber or in other blowers a 50 mg pinch of the bulk powder is placed in the instrument and the nozzle is introduced well into the nostril and so directed that its tip is pointed upward between the eyes. A few puffs deposit the powder on the mucous membrane the anterior portion of the naso-

pharyngeal roof being covered. The remainder of the powder is then blown into the opposite nostril. Too vigorous blowing is avoided as it scatters the powder to non-absorbing areas. The patient experiences a slight stinging sensation "between the eyes" when the powder is correctly placed and he soon becomes expert in its application. The powder is used at 4 hour intervals during the day and once during the night. Continued use produces no local irritation and allergic manifestations have not been noted. The technic is simple, convenient and without objectionable features. A not inconsiderable feature of powder therapy is the low cost. Intranasal medication is ineffective during a coryza and at such times hypodermic administration of a posterior pituitary preparation is necessary.

Overdosage with posterior pituitary medications will not stop the urinary flow but patients should be cautioned to reduce their fluid intake to normal levels during treatment. The large volume fluid intake necessary with uncontrolled diabetes insipidus may become a habit and if continued during therapy can lead to serious water intoxication. Only enough water to satisfy the thirst should be taken.

Some subjects appear to be sensitive to pituitary preparations and besides severe intestinal cramps and other gastro-intestinal reactions show cardiovascular symptoms. For this reason it is wise to try a patient with a small dose of an aqueous extract before using "pitressin" tannate in oil. When a patient continues to react unfavorably it may be necessary to give more frequent injections of smaller doses of extract. As a rule intranasal insufflation therapy will avoid untoward reactions. This method also is free of the occasional atrophy of subcutaneous tissue around the site of numerous hypodermic injections in the same area. Whether or not the anaphylactoid reactions reported from pituitary extract injections may be avoided by powder therapy has not been noted.

Substitution therapy in diabetes insipidus by means of the antidiuretic hormone in the form of various posterior pituitary preparations is a palliative measure. It should be considered in the same category as the use of insulin in diabetes mellitus. The therapy

in both cases must be continued for the remainder of the patient's life except for the rare cases in which remissions may occur. An exception is in diabetes insipidus secondary to a cause which may be successfully removed or treated.

EATON M. MACHAY

REFERENCES

- Allen F. M. and Sherrill J. W. Diet Treatment of Diabetes Insipidus. *J. Metabolic Research* 3:479 1923
- Blotner H. Pitressin Tannate in Oil in Treatment of Diabetes Insipidus. *J. A. M. A.* 119:995 1942
- Blumgart H. L. Antiduretic Effect of Pituitary Extract Applied Intranasally in a Case of Diabetes Insipidus. *Arch. Int. Med.* 29:508 1922
- Brown W. E. and Ryneanson E. H. A Procedure for the Diagnosis of Diabetes Insipidus. *Proc. Staff Meet. Mayo Clin.* 19:67 1944
- Carter A. C. and Robbins J. Use of Hypertonic Saline Infusions in Differential Diagnosis of Diabetes Insipidus and Psychogenic Polydipsia. *J. Clin. Endocrinol.* 7:753 1947
- Choay A. and Choay L. Traitement du diabète insipide par des prises nasales de poudre de lobe postérieur d'hypophyse. *Presse méd.* 36:1155 1928
- Choay A. and Choay L. Traitement du diabète insipide par des inhalations d'extrait de lobe postérieur d'hypophyse. *Rev. neurol.* 31:267 1924
- Farrar A. and Ceccarom B. Influenza degli estratti ipofisari sull'equilibrio dell'acido ipponico. *Gazz. d. osp.* 34:879 1913
- Greene J. A. and January L. E. Diabetes Insipidus Treated by Subcutaneous Administration of Suspensions of Pitressin Tannate in Oil. *J. A. M. A.* 115:1183 1940
- Hickey R. C. and Hare A. Renal Excretion of Chloride and Water in Diabetes Insipidus. *J. Clin. Investigation* 23:768 1944
- Smith F. M. Diabetes Insipidus Treatment by Intranasal Insufflation of Foster or Lobe Pituitary Powder. *J. A. M. A.* 102:660 1934
- Thorn G. W. and Stern K. E. Pitressin Tannate in Diabetes Insipidus. *J. Clin. Endocrinol.* 1:680 1941
- Verney E. B. Croonian Lecture. Antidiuretic Hormone and Factors which Determine its Release. *Proc. Roy. Soc. London* B 135:25 1947
- Verney E. B. Absorption and Excretion of Water Antidiuretic Hormone (Sharpey-Schafer Membrane Lecture. Abridged). *Lancet* 2:739 1941
- Von den Velden R. Die Nierenwirkung von Hypophysenextrakten beim Menschen. *Berlin klin. Wchnschr.* 50:2053 1913
- Weil A. Ueber die hereditäre Form des Diabetes insipidus. *Deutsches Arch. f. klin. Med.* 93:180 1908
- Weir J. F. Influence of Pituitary Extract on Metabolism in Diabetes Insipidus. *Arch. Int. Med.* 32:617 1923
- Williams R. H. and Henry C. Nephrogenic Diabetes Insipidus Transmitted by Females and Appearing during Infancy in Males. *Ann. Int. Med.* 27:84 1947

ACIDOSIS AND ALKALOSIS

Physiologic Considerations as Related to Therapy. Acidosis and alkalosis refer to disturbances of the acid base balance in the organism. For practical purposes these terms correspond to acidemia and alkalemia. A condition of extravascular acidosis or alkalosis may exist in various tissues for a limited time but by and large the reaction of the blood is representative of the alkalinity or acidity of the body as a whole.

The body fluids are all alkaline but so nearly neutral that the total of the basic cations is practically equal to the sum of acid anions. In the plasma and other extracellular fluids sodium is the chief base normally comprising 92 per cent of the cations. The balance is made up of potassium, cal-

second (22 per cent) while sulfates, phosphates and proteins constitute the remainder. It is obvious then that in acid base disturbances we are primarily concerned with the amount of sodium chloride and bicarbonate in the plasma.

The acid base reaction or pH of the plasma is protected by the buffer salts of weak acids chiefly proteins, bicarbonate and phosphate which can react with strong acids (e.g., HCl, lactic, ketone bodies) to give a neutral salt and a weak acid. Increased respiratory output of CO₂ reduces the carbonic acid con-

against extra base the respiratory output of

immu the sec

in metabolism. The kidneys are responsible for remedying the major disturbances in the acid base balance. They do this first by excreting different ratios of secondary and primary sodium phosphate, depending on

whether base or acid should be lost by the organism and giving wide variations in the reaction of the urine. Excess in organic base, usually sodium, may be excreted as bicarbonate without the loss of plasma anion to the body. Lastly the kidney may rid the body of excess acid by excreting ammonia with it in place of inorganic base.

The mechanisms which protect the reaction of the blood always require some time for their effect and if the disturbance is severe enough the compensating devices are unable to cope with it. Conditions of acidosis and alkalosis then result. The various mechanisms producing acidosis and alkalosis will be outlined for these disturbances are best treated by removing the cause.

Acidosis Acidosis is caused first by a primary CO_2 excess due to increased CO_2 production in the tissues and/or diminished CO_2 output from the lungs. This type of acidosis occurs in morphine poisoning and similar depressions of the respiratory center when inadequate pulmonary ventilation leads to CO_2 retention. This is also seen in a mild way during normal sleep and causes the usual acidity of night urine.

In congestive heart failure pulmonary edema sometimes fails to allow the normal CO_2 loss through the alveoli.

Some cases of emphysema and bronchitis have an abnormally high alveolar CO_2 tension. This in turn increases the blood CO_2 and being a chronic condition is compensated for by an increased bicarbonate content of the blood.

An acid excess due to an increase of acids stronger than carbonic with a compensatory secondary CO_2 deficit is the second cause of acidosis. Typical examples of this type of acidosis are the accumulation of organic acids such as formic in methyl alcohol poisoning, lactic acid in severe exercise, the ketosis of starvation, and acidosis in uncontrolled diabetes also due to the ketone bodies.

Acidification with ammonium chloride in diuretic therapy purposely produces this type of acidosis. The retention of nonvolatile acids such as phosphoric in renal insufficiency has a similar effect so far as the production of acidosis is concerned.

Acute diarrhea, particularly in infants, often produces an acid retention acidosis. It

depends on the relative loss of water and salt. When water loss predominates anhydremia causes renal failure and phosphate retention.

The excessive administration of intravenous saline may cause an acidosis. Sodium occurs in the plasma as the chloride and bicarbonate. When fluid loss is restored with sodium chloride solution, the acidity of the plasma becomes increased as the percentage of bicarbonate decreases. The excretion of an acid urine to remove the excess chloride is necessary to restore the bicarbonate.

A reduction of base with a compensatory secondary CO_2 deficit is the third type of acidosis. This type is uncommon but may occur in acute diarrhea when more salts than water are lost in the feces.

Alkalosis Alkalosis is frequently due to a primary CO_2 deficit resulting from diminished CO_2 production and/or increased CO_2 output. The latter is the most common.

Hyperventilation at rest washes out an excessive amount of CO_2 and lowers the CO_2 tension of arterial blood. This sometimes occurs in hysteria, neurasthenia and other functional nervous disorders as well as in certain organic diseases of the nervous system which involve the region of the hypothalamus.

Hyperpnea due to exposure to high temperatures easily produces such an alkalosis.

Anoxia at high altitudes, and more commonly in cardiac failure, often results in hyperventilation sufficient to induce an alkalosis.

An acid deficit with the loss of acids stronger than carbonic and a compensatory secondary CO_2 excess also causes alkalosis.

Possibly the commonest example of the above is the chloride deficit which occurs when HCl is lost into the stomach and vomitus in high intestinal or pyloric obstruction.

Vomiting of any duration from various causes usually leads to chloride loss and alkalosis.

An increase of base with secondary CO_2 excess is a common form of alkalosis particularly in the past with excessive alkali therapy in peptic ulcers. It is still seen not only as a result of alkali therapy but from the common use of alkalis by the laity for "indigestion and acid stomach."

As emphasized above the therapy of acidosis and alkalosis in most cases is a question of dealing with the cause. There are a few instances where direct therapy is indicated. Acidosis due to primary CO_2 excess can be treated only indirectly and oxygen therapy is useful in a number of cases (e.g. congestive heart failure).

(s
ca

pressed too far it is simply discontinued. The retention acidosis of renal insufficiency is part of the picture of renal failure. Uremia however does not consistently present an acidosis. Emesis is common and acid loss from the stomach via this route may compensate for the retained acid anions and even cause an alkalosis.

Uncontrolled diabetes and starvation frequently result in a ketone body acidosis (ketosis). Diabetic acidosis is controlled by the use of insulin and diet rarely with the use of alkali. It is the result of the failure to store and use glucose normally so that a high level of fat metabolism ensues. The ketone bodies are produced in the liver and carried elsewhere for combustion. Being acid and stronger than bicarbonate they produce the second type of acidosis. In starvation the ketosis occurs because of an absolute lack of glucose. It is a physiologic mechanism which may have ill effects if of high intensity. The starvation may result from vomiting, diarrhea or failure to take food. It is best treated with carbohydrate food in the form of intravenous glucose solution if necessary. Alkali therapy if it is indicated at all should be used in babies or small children with ketosis: 1000 cc of $\frac{1}{4}$ molar

sodium lactate solution by the intravenous route is preferred. The lactate is metabolized and the effect is the same as administering sodium bicarbonate solution without the disadvantages of its instability. As a rule alkali is unnecessary and normal saline will suffice to restore the fluid loss and overcome dehydration produced by acidosis.

Alkalosis resulting from a primary CO_2 deficit caused by hyperventilation may be controlled by having the subject rebreathe into a paper bag from time to time. The chief use of this procedure is to aid the neurasthenic in controlling and understanding his symptoms. As in all types of alkalosis the immediate problem is to prevent the tetany which occurs following a fall in the ionization of calcium as the pH of the plasma is raised.

The alkalosis of intestinal obstruction is a secondary disturbance. If surgery is not indicated immediately the loss of acid and base through the vomitus or into the gastrointestinal tract may often be controlled if no food or fluid of any kind is taken by mouth. The restoration of the salt and water in any case is best done with ordinary saline solution administered intravenously. Glucose is also useful because the lack of food dehydration and even the alkalosis may promote a ketosis. A ketosis is not always an acidosis and if present from glucose lack may be enhanced by an alkalosis.

Alkali therapy may cause a serious alkalosis. Discontinuing the alkali is usually the only necessary step but on occasion renal failure supervenes and it is desirable to give small doses of ammonium chloride as an acidifying salt.

EATON M. MACKEY

DISEASES OF THE GLANDS OF INTERNAL SECRETION

ADDISON'S DISEASE

With the newer methods of treatment the life of the patient with Addison's disease has been extended several years. The improved outlook is a tribute to the many workers in the fields of biochemistry and clinical research even though our treatment is mainly substitutive in type. The treatment of patients requires an understanding of the pathologic physiology, for the use of the various therapeutic measures is governed by knowledge of the altered physiologic disturbances.

The important guides to adequate treatment are clinical symptoms and progress, i.e., weakness, gastrointestinal symptoms, appetite changes in body weight, fluctuations of blood pressure, pulse, and laboratory findings i.e., blood hematocrit readings, blood urea nitrogen, blood sugar determinations, and blood sodium determinations. It must be re-emphasized that though we have effective therapeutic agents they are not in

may be able to lead a normal existence, if not unduly subjected to stresses and strains, on simple dietary management including an increase in daily salt intake. Such patients, however, are potentially in danger of crisis

ing danger. The clinician must always bear in mind that he is dealing with a chronic illness, which at any moment may become seriously acute. He must present an understanding of the disease to the patient, but not in such a manner that a heavy burden is made more unbearable.

Understanding of the life situation, the patterns in the patient's behavior which

might be present that could not withstand added insult, must always be considered in presenting to the patient the management of his illness and what to watch for in symptoms. The patient should be taught the stresses and strains which could precipitate symptoms of the disease: overexertion in sections, exposure to marked changes in temperature, injuries, irregularity in food intake. He should be taught the symptoms that are warning signs and to report to his physician questionable symptoms that he does not understand. These should be taught as thoroughly to the patient as they are taught to the medical student in the classroom.

In general it is advisable to teach the technic of intramuscular injections even though injections may not be needed at the time of instruction. This will enable the patient to use the syringe and needle when necessary.

DIETARY MANAGEMENT. A diet adequate in calories to maintain optimal weight, high in protein and carbohydrate and low in fat which is given usually in three feedings and

able foods, then protein can be administered in the form of powdered amino acids and protein hydrolysates given in milk and tomato juice.

Although the use of low potassium diets (16 to 20 gm) has been advocated in the past at the Mayo clinic by Ryncarson and his co-workers, the availability of adrenal

tion such diets were once used. Most patients found this restricted diet unpalatable and its method of preparation troublesome. With the advent of desoxycorticosterone acetate

and the more potent adrenal cortical extracts patients report that they would prefer the daily hypodermic injection of hormones rather than be restricted so markedly in their food intake. Most patients also report a sense of well being while on specific hormone therapy that they do not have on dietary management with increased salt intake. The dangers of the decreased potassium diet while on desoxycorticosterone acetate will be discussed later.

Increased Salt Intake The average American diet contains about 5 gm. of NaCl per day. In attempting to maintain the patient on salt alone it is necessary to add an additional 10 to 20 gm. daily. The simple statement to the patient that he should salt his food heavily is not a safe procedure for the quantity may fall short of what is needed to maintain a normal electrolytic pattern. The salt is best prescribed in the form of enteric coated tablets taken several times during the day. It must be kept in mind that nausea, vomiting and diarrhea may be produced by excessive salt intake.

CORTICAL EXTRACT Adrenal cortical extract is usually taken intramuscularly or subcutaneously by the patient in doses of 2 to 5 cc. usually divided into two doses during the day. It is given at the time of crisis intravenously but its effectiveness by this route of administration is transitory. In contrast to desoxycorticosterone acetate there is no danger of overdosage and never any danger of hypertension. The use of this excellent preparation is limited because of expense. Some patients need as much as 50 cc. per day. It is advisable to use increased salt with the use of cortical extract and thus cut down the amount of the latter necessary. Whole extract has an effect on the hypotension indirectly by improving the patient generally.

Whole adrenal cortical extract has an added feature in that it has an effect on carbohydrate metabolism. Beef adrenal cortical extract has a relatively slight and transient effect on the blood sugar. Pork adrenal cortical extract has a direct action on carbohydrate metabolism that is greater than beef adrenal cortical extract and tends to correct the blood sugar abnormalities of Addison's disease.

DESOXYCORTICOSTERONE ACETATE (*Intramuscularly*) Satisfactory management of Addison's disease has been obtained by the *intramuscular injection of desoxycorticosterone acetate*. It can be given subcutaneously but it is never given intravenously for it is put up in sesame oil. The average dose is from 1 to 5 mg. daily intramuscularly usually in one dose. At times of stress the dose may be increased to as high as 25 mg. per day but one must watch carefully for rapid gain in weight, edema or rise in blood pressure. There are some patients who need the injection every other day or every third day.

Pellets Pellets are never inserted in the early stages of the management of Addison's disease. During the first few months of treatment with synthetic hormone a gradual decrease in the patient's requirement of hormone usually ensues. As the patient's clinical and electrolyte pattern improves the requirement decreases. Usually the patient is treated for at least 3 months with intramuscular injections before pellets are inserted and then only when the intake of NaCl has been relatively constant for this period of time. The use of pellets is economical and has the same effect as when the synthetic hormone is given intramuscularly. The average duration of a pellet implant is from 10 to 13 months.

The control of the hormone by this method is more difficult for if there is overdosage the patient will need surgical intervention. It is wiser to implant less than necessary and supplement with intramuscular injections when necessary. Patients over 40 are poor subjects for implantation for they have a tendency to increased blood pressure and angina. Patients in this age group need more frequent readjustments of dosages than in the younger group.

usually 60 to 75 per cent of that dosage required by injection. Thus if a patient needs 5 mg. of desoxycorticosterone acetate per day he would need to have 10 pellets inserted to get 30 mg. per day.

Implantation is a minor surgical procedure. The pellets are implanted in the infra-scapular region under local anesthesia with

■ special trocar designed for this purpose

SUBLINGUALLY Desoxycorticosterone acetate in propylene glycol may be used sublingually. The preparations usually employed contain 10 mg per cubic centimeter and are given in divided doses of 0.1 cc each. The objections to this form of therapy are that three to five times as much of the synthetic hormone ■ needed when taken in this form as when taken by injection. Sublingual desoxycorticosterone ■ needed several times during the day and must be kept sublingually for 5 minutes which some patients find difficult to do. Moeblig reported swelling of the submaxillary glands following this method of administration.

INTRA ORAL ADMINISTRATION Anderson and co workers have used intra oral administration of desoxycorticosterone acetate since 1940. Because the mixture of synthetic hormone used sublingually needed meticulous care in handling they employed as a solvent a polyethylene glycol wax of high molecular weight which was solid at body temperature. A tablet containing 20 mg of hormone was placed inside the cheek. The tablets slowly disappeared in an hour. Fourteen patients with Addison's disease have been reported managed by this group with this form of therapy.

Dangers and Disadvantages There is definite danger from overdosage with the synthetic hormone. Hypertension, pulmonary and peripheral edema and congestive heart failure have been reported with fatalities. Muscular weakness and paralysis associated with fall in serum potassium are also known to occur when there has been a curtailment in the amount of potassium in the diet. For this reason there should be no limitation of potassium intake in the diet when desoxycorticosterone acetate ■ used. Forster and his associates have found some degenerative lesions in the cerebral arteries while other arteries studied have failed to reveal any changes in patients treated with the synthetic hormone. Local irritation due to the sesame oil may be an annoying factor with intramuscular injection. The treatment for overdosage ■ reduction in the size of the dosage of the hormone, the withdrawal of NaCl and occasionally the administration of potassium salts usually 10 to 20 cc of a 10 per cent solution of potassium citrate

which may be added to any palatable fruit drink.

IMPLANTATION OF A GRAFT Broster and his co workers described a case in which a hypertrophied adrenal gland from a patient suffering from the adrenogenital syndrome was grafted by vascular anastomosis into ■ patient suffering with Addison's disease. Fourteen months after operation the patient had been without substitution therapy for 7 weeks and had shown no symptoms of adrenal insufficiency. This mode of treatment is certainly the ideal method. Effort should be continually directed toward this more physiologic type of therapy.

USE OF OTHER ENDOCRINE PRODUCTS Williams and his co workers made a study of 5 patients with Addison's disease with the objective of producing a clinical improvement superior to that obtained with desoxycorticosterone acetate alone, particularly with regard to the patient's muscular strength. Testosterone propionate improved the strength, slightly to moderately. However, after the patient had worked a few hours he noticed more definite fatigue than normal. The deficiency of the corticosterone is regarded as the probable cause of this fatigue.

CORTISONE Thorne has recently advocated the use of 17 hydroxy 11 dihydrocorticosterone (cortisone) in patients with adrenal insufficiency. Because of this hormone's ability to aid in the regulation of carbohydrate metabolism it ■ a valuable adjunct to therapy with desoxycorticosterone. After careful regulation of the dosage of cortisone by administering 10 to 20 mg of cortisone in oil daily pellets of cortisone are implanted subcutaneously in a quantity calculated to release 10 to 20 mg of the hormone per day. Reimplantation of cortisone pellets must be repeated every 2 to 3 months.

The Management of Acute Adrenal Insufficiency The proper care of the patient with adrenal crisis embodies the understanding of the altered physiologic status and the use of our armamentarium of substitutive therapy. The state of shock with the dehydration and circulatory collapse demands the immediate institution of emergency measures. At once the patient must be started on 5 per cent glucose in saline intravenously with the concomitant adminis-

tration of 50 to 100 cc of adrenal cortical extract intravenously. At the same time the patient should be given 25 to 50 cc of adrenal cortical extract intramuscularly as well as 10 to 20 mg of desoxycorticosterone acetate intramuscularly. Epinephrine both the aqueous and in oil may be used in combating the shock.

The patient in adrenal crisis must have constant attendance. Therapy does not end with the institution of the above measures but continues throughout the critical period by constant observations of the blood pressure, pulse, blood urea nitrogen, blood sugar, sodium and chloride determination. The clinical status is observed most critically especially the lungs for signs of congestive failure for too much desoxycorticosterone acetate or too rapid an inflow of intravenous fluids may throw the patient into pulmonary edema.

A continuous intravenous drip of 5 per cent glucose and saline is continued until the patient is able to take nourishment by mouth and all the gastro intestinal symptoms have subsided. The amount of saline to be given can be determined only by observation of the patient. It may be necessary to give whole adrenal cortex intravenously as often as every hour. There is no danger from over dose of this preparation in contrast to the danger with desoxycorticosterone acetate. The chief objection to the use of whole adrenal cortex is its costliness. This should never be a consideration in so critical a picture. When the tide of crisis has turned the intervals between dosages of whole adrenal cortex may be increased and the amount given may be gradually decreased.

In contrast the amount of synthetic hormone given must be gauged most carefully. Usually an interval of 10 to 12 hours may elapse between dosages of intramuscular desoxycorticosterone acetate. Epinephrine is usually needed only at the onset of management of the shock picture. Transfusion of whole blood or plasma may be used to combat the severe circulatory collapse.

The change of management from the massive therapy as outlined above to a regimen designed for the maintenance of the patient in the normal routine of his life is a gradual one. The ultimate goal is the use of substitutive therapy in the form most

acceptable to the patient and his economic status which is always a factor with costly medications. The change to the newer regimens can be guided only by the meticulous observation of the clinical and laboratory findings.

The Management of Acute Infections in Addison's Disease. Any infection is of grave importance in a patient with Addison's disease even a mild upper respiratory infection. These patients notoriously have poor

patients report mild symptoms to their physician and immediately fortify themselves with an increase in salt intake and an increase of hormone by injection. Antibiotics and chemotherapy are usually started earlier in these patients than in usual with other individuals.

The Management of Surgical Conditions in Addison's Disease. In spite of our armamentarium of substitutive therapy

period during which the patient should receive 25 to 50 cc of whole adrenal cortex per day given subcutaneously in divided dosage. Desoxycorticosterone acetate in dosages from 5 to 15 mg may be given intramuscularly each day. Every effort must be made room in and with pattern

of crisis is ever present just before surgery during the operation and immediately after the operation 25 to 50 cc of whole adrenal cortical extract should be given intravenously along with a constant intravenous drip of glucose and saline. Spinal anesthesia should be avoided; patients with Addison's disease tolerate inhalation anesthesia better. Wherever possible local anesthesia should be used.

The Management of Pregnancy in Addison's Disease. The first trimester of pregnancy carries with it the danger of nausea and vomiting. The inability to maintain adequate nutrition under these circumstances may precipitate a crisis. It is well

then, to fortify the patient with multiple doses of whole adrenal cortical extract daily along with desoxycorticosterone acetate. During the remaining trimesters there is constant need for supervision of the salt intake and desoxycorticosterone acetate dosage, for with the rise in circulating estrogen and progesterone, with their ability to help retain sodium in the body, plus whatever hormone comes from the fetus, there may be danger of hypertension and edema. During the actual management of delivery, however, the patient should be treated as if in crisis. This type of management should be kept up in the postpartum period and gradually the dosages of whole adrenal cortical extract and desoxycorticosterone acetate decreased until all danger has passed.

M DAVID ALLWEISS

REFERENCES

- Anderson, E., Haymaker, W. and Henderson E. Successful Sublingual Therapy in Addison's Disease *JAMA*, 115:167, 1940
- Anderson, E., et al. The Intracortical Administration of Desoxycorticosterone Acetate Tablets in the Treatment of Addison's Disease *J Clin Endocrinol*, 8:884, 1948
- Broster, L. R., and Gardiner Hill H. Case of Addison's Disease Successfully Treated by Graft *Brit M J*, 2:570, 1946
- Conference on Therapy Treatment of Addison's Disease *JAMA* 122:2511, 1939
- Council on Pharmacy and Chemistry New and Nonofficial Remedies *JAMA* 139:849, 1949
- Duncan, G. G. (Editor) *Diseases of Metabolism, Detailed Methods of Diagnosis and Treatment, A Text for the Practitioner* Philadelphia W B Saunders Company 1947
- Ferrebee, J. W., et al. Desoxycorticosterone Esters,

- Certain Effects in Treatment of Addison's Disease *JAMA*, 113:1725, 1939
- Forster, F. M., et al. Degenerative Changes in Cerebral Arteries Following Administration of Desoxycorticosterone Acetate *J Clin Endocrinol*, 6:77, 1946
- McBryde, C. M., and de la Balze, F. A. Pork Adrenal Cortex Extract, Effect upon Carbohydrate Metabolism and Work Capacity in Addison's Disease *J Clin Endocrinol*, 4:287, 1944
- Moehlig H. C. Addison's Disease Followed for 9 Years Case Report with Autopsy *J Clin Endocrinol*, 7:134, 1947
- Ryneerson, E. H. Treatment of Addison's Disease *JAMA*, 111:897, 1938
- Soffer, L. J., Engel, L. F., and Oppenheimer, B. ■ Treatment of Addison's Disease with Desoxycorticosterone Acetate By Intramuscular Injections and Subcutaneous Implantation of Pellets *JAMA*, 115:1860, 1940
- Thorn, G. W. Treatment of Addison's Disease *J Clin Endocrinol*, 1:76, 1941
- Thorn, G. W., and Frier, W. M. Desoxycorticosterone Acetate Therapy in Addison's Disease Clinical Considerations *JAMA* 114:2517, 1940
- Thorn G. W., Dorrance S. S., and Day, E. Addison's Disease, Evaluation of Synthetic Desoxycorticosterone Acetate Therapy in 158 Patients *Ann Int Med*, 16:1053, 1942
- Thorn, G. W., Howard, R. P., and Emerson K., Jr. Treatment of Addison's Disease with Desoxycorticosterone Acetate, Synthetic Adrenal Cortical Hormone (Preliminary Report) *J Clin Invest* 18:449, 1939
- Thorn G. W., et al. Treatment of Addison's Disease with Pellets of Crystalline Adrenal Cortical Hormone (Synthetic Desoxycorticosterone Acetate) Implanted Subcutaneously *Bull Johns Hopkins Hosp*, 64:339, 1939
- Wilder, R. M., et al. Control of Addison's Disease with Diet Restricted in Potassium Clinical Study *Proc Staff Meet, Mayo Clin*, 11:273, 1936
- Williams R. H., et al. Treatment of Adrenal Insufficiency *J Clin Endocrinol* 5:163, 1945
- Willson, D. M., Ryneerson, E. H., and Dry, T. J. Cardiac Failure Following Treatment of Addison's Disease with Desoxycorticosterone Acetate *Proc Staff Meet, Mayo Clin*, 16:163, 1940

THYROID DISEASES

HYPERTHYROIDISM

The introduction in 1943 of new and potent antithyroid drugs did, for a time, tend to upset the standard and accepted methods of treating hyperthyroidism. It was suggested by some and, of course, sincerely hoped for by those interested in hyperthyroidism, that these new substances would accomplish a medical cure for this disease and that the era of thyroidectomy was soon

to pass. Sufficient time has now elapsed and clinical trial of the new goitrogens has been sufficiently widespread to permit an understanding of their true value so that now again we can establish a practical plan for the therapy of hyperthyroidism. Unfortunately, we may soon again be thrown into a state of confusion concerning therapy with the advent of radioactive iodine which at the present time is undergoing experimental study. Because of the problems concerned

with the use of radioactive iodine and because of its potential dangers however it will be some time before the exact therapeutic place for this agent is established

A practical approach to the treatment of

enlarged thyroid (3) recurrent hyperthyroidism (after thyroidectomy) and (4) relapsing hyperthyroidism after antithyroid (drug) treatment

that the diagnosis of hyperthyroidism be definitely established before treatment is begun and should there be any doubt it is preferable that the patient be given a period of observation since hyperthyroidism is not a static disease and if one waits sufficiently long the diagnosis usually becomes evident

Once the diagnosis of hyperthyroidism is established the next step deals with the decision as to the type of goiter present whether it is primary hyperthyroidism (exophthalmic goiter—diffuse hyperplasia) or adenomatous goiter with hyperthyroidism (toxic nodular goiter). This differentiation of hyperthyroidism is necessary since the response to treatment to be expected depends on the type of goiter. For instance the symptoms of adenomatous goiters are rarely benefited by Lugol's solution whereas in primary hyperthyroidism improvement (rarely complete) can always be expected. Ultimate and decisive treatment is advisable for adenomatous goiter and subtotal thyroidectomy is indicated whereas some patients with mild primary hyperthyroidism may obtain a cure or prolonged remission following treatment with iodine alone. Again when the antithyroid drugs are used (thiouracil, propylthiouracil, methylthiouracil, etc.) it is found that a patient with primary hyperthyroidism responds more readily to a given dose than does a patient with adenomatous goiter with hyperthyroidism; the latter requires about twice the time for reduction of an equally elevated basal metabolic rate to normal. Therefore in discussing the treatment of hyperthyroidism a careful distinction will be made of the two types of the disease classified as primary hyperthyroidism (exophthalmic goiter) and adenomatous goiter with hyperthyroidism.

Under primary hyperthyroidism are grouped (1) mild hyperthyroidism with slight thyroid enlargement, (2) moderate to severe hyperthyroidism with definitely

treatment with Lugol's solution alone. A daily dose (10 drops) of Lugol's solution accomplishes in a few weeks complete relief of symptoms and a return of the thyroid to normal size but with perhaps firmer consistency. That this represents a cure of the hyperthyroidism is unlikely, but many patients may remain symptom free for years. This assumption is borne out by the history which hyperthyroid patients frequently reveal of similar complaints, weight loss and nervousness which subsided after iodine treatment given years before. Patients who are given iodine as the sole therapy must be advised that one cannot predict with certainty if the treatment will be immediately successful and if successful whether the thyroid overactivity will remain cured or recur at some time in the future. Therefore when embarking on iodine therapy patients must be kept under observation and suitable steps must be taken if the hyperthyroidism is not completely controlled. Complete control includes relief of all symptoms and return of the weight and the metabolic rate to normal. If after 3 months of daily administration of iodine the patient is not well iodine therapy must be abandoned and more energetic treatment instituted since such a patient is no longer to be considered as having mild hyperthyroidism.

Patients with mild hyperthyroidism can also be given a trial of treatment with the new antithyroid drugs. Thiouracil in a daily dose of 600 mg or 300 mg of propylthiouracil daily should be continued until the basal metabolic rate reaches normal at which time the dose of medication should be halved. Treatment should be continued and complete control maintained for a period of 3 to 6 months, the dosage being further reduced if control seems satisfactory. At the end of 3 to 6 months treatment is discontinued and the patient is observed every 1 to 2 months for possible relapse of hyperthyroidism. This type of therapy is also trial treatment and patients must be aware of the

with the use of radioactive iodine and because of its potential dangers however it will be some time before the exact therapeutic place for this agent is established.

A practical approach to the treatment of a given case of hyperthyroidism is dependent on a number of factors which must be given sufficient consideration before proceeding with treatment. It is of course essential that the diagnosis of hyperthyroidism be definitely established before treatment is begun and should there be any doubt, it is preferable that the patient be given a period of observation since hyperthyroidism is not a static disease and if one waits sufficiently long the diagnosis usually becomes evident.

Once the diagnosis of hyperthyroidism is established the next step deals with the decision as to the type of goiter present whether it is primary hyperthyroidism (exophthalmic goiter—diffuse hyperplasia) or adenomatous goiter with hyperthyroidism (toxic nodular goiter). This differentiation of hyperthyroidism is necessary since the response to treatment to be expected depends on the type of goiter. For instance the symptoms of adenomatous goiters are rarely benefited by Lugol's solution whereas in primary hyperthyroidism improvement (rarely complete) can always be expected. Ultimate and decisive treatment is advisable for adenomatous goiter and subtotal thyroidectomy is indicated whereas some patients with mild primary hyperthyroidism may obtain a cure or prolonged remission following treatment with iodine alone. Again when the antithyroid drugs are used (this

enlarged thyroid (3) recurrent hyperthyroidism (after thyroidectomy) and (4) relapsing hyperthyroidism after antithyroid (drug) treatment.

Mild Hyperthyroidism An occasional patient with mild hyperthyroidism and only slight thyroid enlargement is amenable to treatment with Lugol's solution alone. A daily dose (10 drops) of Lugol's solution accomplishes in a few weeks complete relief of symptoms and a return of the thyroid to normal size but with perhaps firmer consistency. That this represents a cure of the hyperthyroidism is unlikely but many patients may remain symptom free for years. This assumption is borne out by the history which hyperthyroid patients frequently reveal of similar complaints weight loss and nervousness which subsided after iodine treatment given years before. Patients who are given iodine as the sole therapy must be advised that one cannot predict with certainty if the treatment will be immediately successful and if successful whether the thyroid overactivity will remain cured or recur at some time in the future. Therefore when embarking on iodine therapy patients must be kept under observation and suitable steps must be taken if the hyperthyroidism is not completely controlled. Complete control includes relief of all symptoms and return of the weight and the metabolic rate to normal. If after 3 months of daily administration of iodine the patient is not well iodine therapy must be abandoned and more energetic treatment instituted since such a patient is no longer to be considered as having mild hyperthyroidism.

Patients with mild hyperthyroidism can also be given a trial of treatment with the new antithyroid drugs. Thiouracil in a daily dose of 600 mg. or 300 mg. of propylthiouracil daily should be continued until the basal metabolic rate reaches normal at which time the dose of medication should be halved. Treatment should be continued and complete control maintained for a period of 3 to 6 months the dosage being further reduced if control seems satisfactory. At the end of 3 to 6 months treatment is discontinued and the patient is observed every 1 to 2 months for possible relapse of hyperthyroidism. This type of therapy is also a trial treatment and patients must be aware of the

a given dose than does a patient with adenomatous goiter with hyperthyroidism the latter requires about twice the time for

of the disease classified as primary hyperthyroidism (exophthalmic goiter) and adenomatous goiter with hyperthyroidism.

Under primary hyperthyroidism are grouped (1) mild hyperthyroidism with slight thyroid enlargement (2) moderate to severe hyperthyroidism with definitely

high possibility of failure Since these antithyroid drugs cannot be administered without possible danger observation every 2 to 3 weeks is necessary at which time leukocyte and differential blood counts are determined Patients must be acquainted with the type of reactions (fever sore throat and skin rash) which may develop following the use of these drugs and advised to notify the physician at once should any such untoward sign or symptom develop

thyroid drugs followed by a carefully executed subtotal thyroidectomy This offers the patient prompt and decisive treatment and cure with a minimum of risk and eliminates the great chance of failure which is inherent in using antithyroid drugs in this type of hyperthyroidism with the hope of inciting a remission of the disease The disadvantages of maintenance treatment with antithyroid drugs are real and will be given consideration later in this discussion

Once the diagnosis of moderate to severe primary hyperthyroidism is established and a thyroidectomy is deemed advisable a program of antithyroid treatment is planned The duration of treatment prior to thyroidectomy depends on factors such as the level of basal metabolic rate duration of hyperthyroidism previous iodine administration age of the patient degree of physical depletion and status of the cardiovascular system Experience in preparing some 1900 hyperthyroid patients for thyroidectomy has revealed that the average patient with primary hyperthyroidism will obtain a daily drop of 1 per cent in the basal metabolic rate when receiving 600 mg of thiouracil or 200 to 300 mg of propylthiouracil or methylthiouracil a day The 300 mg dose of propylthiouracil or methylthiouracil is limited to those patients with large goiters Therefore if a patient has a basal metabolic rate of plus 50 one can predict that 7 weeks of treatment will be required to return the metabolic rate to within a normal range Previous administration of iodine will delay response to treatment and in these cases 2 or 3 weeks must be added to the prediction time In the presence of advanced age long standing disease or cardiovascular complications (to be

discussed later) it is not enough to return the metabolic rate to normal but maintenance treatment with halving the dose of the antithyroid drug should be continued until normal compensation has been restored and operative risk avoided Some patients may require as long as 3 to 4 months to accomplish this end and some have been carried on maintenance treatment for as long as a year before it was thought safe to proceed with the operation In addition to the antithyroid drug which is administered in a divided dose at 8 A.M. and 8 P.M. the patient should be advised to follow a program of adequate rest which should depend on his general condition At times a week or 10 days of bed rest is necessary at the beginning of treatment since benefit is rarely noted from treatment before this time Patients are urged to take a diet which is high in carbohydrate and protein in an attempt to regain the weight which has been lost Feedings between meals are also advised Stimulants such as coffee tea and alcohol are discontinued and emphasis is given to avoidance of tobacco since smoking has been observed on many occasions to retard the expected recovery Patients with associated heart disease are given the usual cardiac treatment with a maintenance dose of digitalis Medication other than antithyroid drugs digitalis and occasionally vitamins should be avoided so that should any reactions occur one can be certain as to the offending agent Occasionally phenobarbital $\frac{1}{4}$ grain (15 mg) four times a day may be necessary at the beginning of treatment to control undue nervousness and to induce sleep

therapy until myxedema develops since this clinical state causes an increase in the operative risk Patients with myxedema are sensitive to narcotics This sensitivity results in decrease in respiratory rate and cough reflex which in combination with the laryngeal edema of myxedema and that following thyroidectomy may lead to serious respiratory complications and at times tracheotomy becomes necessary Therefore should myxedema occur antithyroid treatment must be withdrawn and thyroidectomy postponed until euthyroidism is present

Experience with many patients receiving antithyroid drugs has revealed the occasional patient who, although she has a normal basal metabolic rate, has objective evidence of myxedema such as lid edema, puffiness of the face, and an elevated blood cholesterol. This development makes it necessary for the physician to be aware of the possibility of myxedema following administration of these drugs and to determine the blood cholesterol level for confirmation of the diagnosis.

In addition to the antithyroid drugs preoperatively Lugol's solution must be given to bring about involution of the thyroid gland in preparation for thyroidectomy. Suitable involution is obtained when iodine is given during the last 3 weeks of treatment in combination with the antithyroid drug. Lugol's solution 10 drops is given once a

onset of treatment. The rapid effect of iodine will usually lessen the thyrotoxicosis. The iodine should be discontinued after 7 to 10 days and resumed again 3 weeks before thyroidectomy. Since administering Lugol's solution after operation, immediately or for some months has not been proved to be of certain value we have not resorted to its use.

It must be admitted that primary hyperthyroidism can be kept under complete control by an adequate daily dose of any of the available antithyroid drugs. The maintenance dose of the antithyroid drug must be decided in each case by a program of trial and error, that is, by gradually reducing the daily dose to a point short of relapse of the hyperthyroidism. Maintenance treatment does carry with it many valid disadvantages which must be considered when this type of therapy is undertaken. Chief among these are the problems entailed in trying to keep any patient on prolonged medical treatment. Patients discontinue treatment for any one of a number of reasons with resulting relapse of hyperthyroidism which many can ill afford, particularly the older patients with associated heart disease. The possibility of toxic reactions is always a hazard which must be considered and should agranulocytosis

develop prompt treatment with penicillin is necessary to avoid a fatality.

Recurrent Hyperthyroidism Recurrent hyperthyroidism (after subtotal thyroidectomy) must be handled individually, according to the circumstances existing in each case. In the presence of mild hyperthyroidism with a small remnant or remnants, the daily administration of 10 drops of Lugol's solution frequently accomplishes full control of hyperthyroidism with disappearance of all symptoms. return of the basal metabolism

little hope of control can be expected from continued or prolonged administration of iodine. The procedure of choice in this situa

of administering the antithyroid drugs as suggested for preparing patients for initial thyroidectomy. Whether these patients with recurrent primary hyperthyroidism will be found to be suitable for radioactive iodine therapy or deep roentgen therapy must be settled following further investigation. A patient with tetany or cord paralysis would seem suitable for some plan of treatment other than surgery. Maintenance treatment with antithyroid drugs may, of course, be used if the problems dealing with its administration are understood and accepted.

Relapsing Hyperthyroidism Relapsing hyperthyroidism after antithyroid treatment is a common problem. Although it was initially reported that antithyroid treatment especially if continued for 11 to 12 months, would give a chance of cure or a remission of hyperthyroidism it is now increasingly evident that this is not the case. Our early reported experience with attempts to bring

agent. The relapse occurred within an average period of 3 months and bore no relation ship to the duration of administration of the antithyroid drug. Most of these patients had primary hyperthyroidism with moderate to large goiters or recurrent primary hyperthyroidism with moderate sized

All of these patients required further therapy, 11 had surgical intervention and one received radioactive iodine. Nine of the 21 patients obtained benefit from the antithyroid treatment which brought about a prolonged remission from the hyperthyroidism. Six of these patients have now been followed for from 4 to 5 years. Two patients had a relapse 4 years after stopping treatment of these one patient remains well by taking Lugol's solution and one patient has had a thyroidectomy.

If a relapse occurs after a period of 3 to 6 months of maintenance of true euthyroidism on antithyroid treatment it is evident that decisive treatment is indicated. In such a situation iodine is not likely to be of value. Maintenance treatment with antithyroid drugs may be carried out but the program of choice is recontrol of hyperthyroidism with antithyroid drugs and thyroidectomy.

Adenomatous Goiter with Hyperthyroidism. This is one type of hyperthyroidism in which preventive treatment is effective. Although the danger of malignant disease in adenomatous goiter is real (6 to 12 per cent) sufficient stress has not been placed on the insidious onset of hyperthyroidism in patients who have had a recognized nontoxic adenomatous goiter for years. However with the increasing age span more attention must be given to the prevention of hyperthyroidism in older patients by urging thyroidectomy in cases of nontoxic adenomatous goiter when operation can be done with complete safety.

When hyperthyroidism develops—and it frequently is insidious in its onset and leads to advanced states of physical depletion and at times serious cardiac complications—the most successful plan of treatment is preparation with antithyroid drugs followed by a subtotal thyroidectomy. Adenomatous goiter with hyperthyroidism is not amenable to control with Lugol's solution and maintenance treatment with antithyroid drugs is not recommended chiefly because of the danger of malignant disease developing in an adenomatous goiter.

The plan of preoperative therapy consists of continuing antithyroid treatment until the

thyouracil or methylthiouracil in a daily dose of 300 mg if continued sufficiently long will bring about a satisfactory result. Experience with many hundreds of cases of adenomatous goiter with hyperthyroidism indicates that 2 days of treatment are required to reduce the basal metabolic rate 1 per cent. With this general rule one can predict the time necessary to restore a patient to euthyroidism. However more time should be taken for those patients with large goiters, those in the older age group and those who show evidence of general debilitation from long standing disease or in whom complications exist. In these the full dose of antithyroid drug should be continued until the basal metabolic rate reaches normal and then a maintenance dose two thirds of the original dose should be continued for months if necessary until the patient's general condition is considered safe for subtotal thyroidectomy. At times it has taken as long as 12 months of preoperative preparation to accomplish the desired degree of improvement. When cardiac conditions are present the usual cardiac measures with digitalization are carried out along with antithyroid treatment. Patients with adenomatous goiter are not given iodine preoperatively. Patients with primary hyperthyroidism since increased vascularity does not result from antithyroid treatment in this type of goiter.

General Problems of Antithyroid Administration. In addition to administering a dose of antithyroid drug which will result in a fall in the basal metabolism to normal the problem of observing patients and acquainting them with the possibility of reactions to these medicines is of real importance if serious complications and deaths are to be avoided. Thiouracil which has almost completely been displaced by propylthiouracil has a reaction incidence of 9 to 10 per cent. The most serious of these is agranulocytosis which has caused deaths. The other reactions such as dermatitis, fever and swollen

are not important but
not Pro
of only
the
the

stantiates them that this substance has a reaction incidence similar to that of thiouracil with agranulocytosis developing with equal frequency. Patients with agranulocytosis if observed early and treated vigorously with penicillin and perhaps streptomycin recover in approximately 8 days. It is therefore essential that each patient receiving these potentially dangerous drugs be carefully observed.

When a patient has a reaction to one antithyroid drug and further antithyroid treatment is necessary it may be possible to shift to another antithyroid drug and continue treatment. We have shifted from thiouracil to propylthiouracil from propylthiouracil to thiouracil or methylthiouracil from methylthiouracil to propylthiouracil or thiouracil. Multiple sensitivities were observed in one patient so that it was necessary to experiment with five antithyroid drugs before one was found which was tolerated. When shifting to another antithyroid drug it is necessary to administer a small test dose (50 mg.) to avoid a serious reaction should the patient prove to be fever or skin sensitive. Continued vigilance is necessary even if a shift at first seems possible since serious blood reactions may suddenly take place soon after the shift is made.

Patients have been observed who tolerated one antithyroid drug in decreasing dose for months and then had a reaction indicating that the duration of treatment or the size of the dose has no relation to the occurrence of a reaction. Again patients have been observed who tolerated one antithyroid drug until treatment was discontinued or lapsed and a few months later had a recurrence of hyperthyroidism which required further antithyroid treatment. They were then found to be sensitive to the drug which was mutually well tolerated. Thus there is evidence that patients may become sensitized to these drugs which is an important point in favor of employing them solely as preoperative agents.

Thyroid Storm. Thyroid crisis or storm is an acute and extremely serious clinical state which occasionally follows thyroidectomy however only in patients who are still hyperthyroid. It may also develop in the event of acute infection in patients with more severe states of thyrotoxicosis. This condition may

rapidly (within 24 to 36 hours) lead to death through an acute hypermetabolic hyperthermic and neurocirculatory upheaval. Since this condition is to be avoided it is essential that no patient with goiter be submitted to thyroidectomy until euthyroidism is accomplished by adequate antithyroid therapy. Also it is not sufficient to reduce the basal metabolism only partially preoperatively as serious crisis reaction may occur even after thyroidectomy in the presence of only mild hyperthyroidism.

Should thyroid crisis develop energetic treatment is necessary and every effort should be instituted at once for little time is available in a condition which usually runs its course in 36 hours. The patient should be placed in an oxygen tent containing a high concentration of oxygen. Restlessness must be controlled by adequate doses of morphine sulfate, $\frac{1}{4}$ grain (15 mg.) every 2 to 3 hours at times being necessary and occasionally intravenous morphine or pentothal is indicated. Fluids must be given in amounts up to 3000 to 5000 cc. in 24 hours by constant intravenous drip. Five per cent glucose in distilled water is alternated with 5 per cent glucose in normal saline solution. Lugol's solution is given daily by placing 30 drops in one of the intravenous infusions. Nasal tube feedings permitting the administration of proteins and additional carbohydrates should also be instituted if fluids and foods are not taken by mouth. Hyperthermia is controlled by local application of ice caps, removal of blankets and I have used to advantage continuous gastric lavage with ice water. The latter measure is continued and repeated to restore the temperature to normal.

Since thyroid storm may be complicated by infection it is advisable that both penicillin and sulfa drugs be given. 100,000 units of penicillin are placed in the initial intravenous infusion and then 50,000 units are given subcutaneously every 3 hours. Sulfa diazine 6 gm. is also added to the initial infusion and 1 gm. every 4 hours thereafter. Excess bronchial mucus is common in this condition. In addition to encouraging the patient to cough and expectorate it may become necessary to aspirate the trachea by direct visualization or by bronchoscopy. This maneuver may correct the accumulation

mucus which would lead to pulmonary atelectasis

Thyrocardiac Disease The problem of the thyroid patient with complicating heart disease has been greatly simplified with the advent of the antithyroid drugs. However, a plea must be made for the prevention or earlier diagnosis of this condition since if a patient with thyrocardiac disease is permitted to go untreated, irreversible cardiac damage may develop and death may occur before adequate antithyroid treatment can be employed or even in spite of antithyroid therapy. Although much has been written urging the removal of adenomatous goiters before the onset of hyperthyroidism we continue to see many patients late in life with advanced thyrocardiac disease. Of these at least 4 patients die yearly in congestive failure or as a result of embolic disease owing to auricular fibrillation before effective antithyroid treatment can be given. Since the thyroid gland of a patient beyond 60 years of age, who develops primary hyperthyroidism is never large averaging 29 gm in weight in a recent study thyroid disease is frequently overlooked in the older age groups because the neck is not carefully examined and the possibility of hyperthyroidism is not considered. Therefore it is essential that hyperthyroidism be considered in older patients who have cardiac symptoms in whom weight loss is a prominent symptom. The earlier thyroid heart disease is diagnosed and treatment begun the less serious is the damage to the heart and the greater will be the ultimate heart reserve.

Before the use of the new antithyroid drugs the operative mortality of thyroidectomy for patients having thyrocardiac disease was 6.6 per cent (1922 to 1941) and of 141 patients who underwent operation from 1937 to 1941 it was 11.3 per cent. Because of the serious operative risk in these patients two stage procedures were necessary in 35 per cent of the cases. In contrast to these figures we now have data on our experience with patients who received antithyroid (thiouracil or propylthiouracil) treatment preoperatively. Of the first 1,000 patients so treated and who had subtotal thyroidectomy, there were 135 patients with thyrocardiac disease. One postoperative death occurred and no patient required a two stage opera-

tion. We have now prepared 1,860 hyperthyroid patients for thyroidectomy, 4 postoperative deaths occurred and all 4 were in patients who had thyrocardiac disease. This indicates that in spite of the most careful preoperative management of the thyrocardiac patient there is still some surgical risk although it has been substantially reduced.

The preoperative management of the thyrocardiac patient must be individualized. Treatment must be prolonged since it does not suffice merely to bring about a euthyroid state preoperatively. It is advisable to maintain a euthyroid state until full cardiac and visceral reserve has returned and only then is the patient ready for thyroidectomy. To accomplish this ideal preoperative state

1 per cent of the patients with auricular fibrillation have a reversal to regular rhythm before thyroidectomy.

Preoperative treatment of the thyrocardiac patient entails antithyroid as well as cardiac measures. The antithyroid drug must be given in a daily dose (propylthiouracil 300 to 400 mg daily) sufficient to return the basal metabolic rate to normal. Patients with large goiters will require even larger doses.

Patients with increased heart rates or fibrillation without congestive failure are not given digitalis until the basal metabolic rate reaches a point near normal since digitalis is of little therapeutic value when hyperthyroidism is still present. Patients with congestive heart failure received combined therapy, cardiac and antithyroid. The cardiac meas-

ures are begun simultaneously with the antithyroid drugs. Patients usually become ambulatory in about 10 days by which time peripheral and pulmonary edema is relieved. Combined treatment is continued until the patient's general condition seems suitable for safe thyroidectomy. If the basal metabolic

rate is normal and heart reserve re established, the risk of thyroidectomy is minimal

Roentgen Therapy in the Treatment of Hyperthyroidism Roentgen irradiation of the thyroid in hyperthyroidism has as its purpose the decrease in the production of excess thyroid hormone. Thus, of course, must be accomplished without serious dam-

is gen
thyroid
r goiter

should not be treated by irradiation since the occurrence of carcinoma in discrete nodular and even in multiple colloid adenomatous goiter is sufficiently high to warrant surgical intervention. Therefore x-ray irradiation should be limited to primary hyperthyroidism. Even this use needs clarification since in our opinion thyroidectomy is the safest and most decisive way of treating primary hyperthyroidism. In practice it has been our policy to limit roentgen therapy to patients with recurrent hyperthyroidism in whom various reasons such as the presence of tetany, recurrent laryngeal paralysis, or previous multiple operations, further thyroid surgery seems inadvisable. Previous administration of Lugol's solution or the new anti-thyroid drugs does not contraindicate irradiation.

Roentgen therapy is given in so called series. The factors used in irradiating the thyroid gland are 200 kv platinum 20 ma 2 mm of copper and 1 mm of aluminum filtration and 50 cm target skin distance. The cone used varies with each patient it should be sufficiently large to cover the gland with irradiation applied through a single anterior or lateral field. An air dose of 300 r is given daily for 6 consecutive days until a total of 1800 r is given. In 2 months if the patient has not reached a euthyroid state a second series of treatment is given. On occasion three series may be necessary. If little response follows the first or second series, it is not likely that roentgen therapy is the treatment of choice in the given case.

Complications such as radiation sickness, transient sore throat erythema of the skin, tracheitis, and esophagitis occasionally occur. The use of heavy filtration and small portals is essential to decrease the chance of permanent skin changes.

It is difficult to determine from the litera-

ture at the Lancy Clinic with patients who have recurrent primary hyperthyroidism has been reviewed by Hare and Salzman and includes 20 such patients in whom the follow up period after irradiation averaged 7 years. The results in these 20 patients were considered good in 18, as interpreted by

Two patients were listed as obtaining poor results.

It is obvious that an insufficient number

patients in whom further thyroid surgical intervention is deemed inadvisable it is worthy of trial and may be met with satisfactory results.

Radioactive Iodine Experience with this potent antithyroid agent has demonstrated its effectiveness in controlling hyperthyroidism. It has not, however, received sufficient clinical trial so that either proper dosage or potential dangers have been fully determined. As yet its use must be strictly limited to research centers where the problems of radioactive isotopes are undergoing controlled investigation. The problems of handling and dispensing radioactive material, protection of workers against harm, and many other difficulties are still to be surmounted.

Thompson et al.

When the radioactive substance is concentrated in the thyroid for concerted action on this gland. Initial experiments on rabbits demonstrated that 30 or 40 days after a subcutaneous injection of I^{131} , fibrosis was present in the thyroid gland and a 50 per cent decrease in size of the thyroid was noted. It is this action of destroying thyroid tissue which is purposely utilized when radioactive iodine is administered to human beings with hyperthyroidism. Difference of opinion exists as to how radioactive iodine is

to be given—in one dose or divided small doses—and how to determine the required dosage to destroy just sufficient thyroid tissue to control the hyperthyroidism and still not induce myxedema. Again, no definite opinion has been reached as to which type of patient with hyperthyroidism is best suited for this form of therapy, that is, should age be a deciding factor, should size limit its use, and many other still unanswered essential questions.

Although there are 11 known isotopes of iodine, only two have been used in therapy, I^{130} , the 12 hour isotope and I^{131} , the 8 day isotope. Both of these radioactive isotopes of iodine emit beta and gamma rays but with different energies and at different rates. The average energy per disintegration of the beta rays expressed in million electron volts, is 0.270 for I^{130} and 0.205 for I^{131} , the

7 per cent

here is the

The thyroid tissue absorbs about 90 per cent of the beta rays but the gamma rays pass through several centimeters of tissue with little absorption and their therapeutic effects are negligible. Because of their penetrability, however, they may be used to measure uptake in the gland by suitable standardized Geiger counters.

Tracer studies using from 50 to 75 microcuries of I^{131} show a variation in the uptake of iodine in various thyroid states. In a normal gland 15 to 30 per cent of the dose is absorbed in 24 hours, in hyperthyroidism, 44 to 76 per cent, and in myxedema 1 to 4 per cent. This uptake is inhibited by previous administration of iodine, such as Lugol's solution, iodized salt, or iodine present in dye used in cholecystography or intravenous pyelography.

The employment of radioactive isotopes as therapeutic agents requires that the radiation dosage be determined. At the present time determination of the proper dose represents the chief problem in utilizing radioactive isotopes, particularly because of difficulty in estimating properly the size of the gland to be treated. This has led toward the plan of repeated small doses instead of a single large dose in attempting to destroy the thyroid gland. The cases reported were given from 4 to as high as 77 millicuries of radioactive

iodine by mouth in an effort to bring about the desired effect.

The general trend of recovery from hyperthyroidism by radioactive treatment is reputed to require about 2 to 3 months and in some cases reported the thyroid gland had returned to an impalpable state. Failures occurred chiefly in patients with high basal metabolic rates.

Certain complications have been reported to follow radioiodine treatment. Reactions such as thyroid storm have followed the use of what was later thought to be an excessive dose. Transient and fixed myxedemas have been noted, the latter in about 12 per cent of the patients treated. Sore throat and cough, lasting for a few weeks, have been reported. Amenorrhea and anemia have also been reputed to occur. Larger series must be treated and carefully followed for at least 5 to 10 years before all the possible reactions to this method of treatment will be known.

ELMER C BARTELS

REFERENCES

- Ba. 8 766 1948
Bartels E C. Thiouracil and Allied Drugs in Hyperthyroidism. *New England J Med*, 233 6, 1948.
Chapman, E M., and Evans, H D. Treatment of Hyperthyroidism with Radioactive Iodine. *JAMA*, 131 88, 1948.
Hare, H F., and Salzman F A. Treatment of Diseases of the Thyroid (In press).
Hertz S., and Roberts A. Radioactive Iodine Therapy in the Study of Thyroid Physiology. *JAMA*, 131 81, 1948.
Soley, M H., Miller E R., and Foreman N. Graves' Disease. Treatment with Radioiodine (I^{131}). *J Clin Endocrinol*, 9 29, 1949.

HYPOTHYROIDISM

The term hypothyroidism may have various interpretations but its use should be strictly limited to cases in which there is unquestioned clinical evidence of thyroid deficiency. Patients with only lowered basal metabolic rates should not be included since it is well recognized that the range of the normal metabolic rate is wide and there are instances of patients with metabolic rates as low as -30 per cent who do not have the

slightest clinical evidence of thyroid deficiency. These patients should not be included in the group with hypothyroidism since they are not benefited by thyroid treatment.

Cases to be included in the classification of hypothyroidism must satisfy the following four criteria: (1) reduced basal metabolic rate, (2) elevated blood cholesterol (myxedema with normal cholesterol does occur occasionally), (3) objective manifestations of thyroid deficiency and (4) unquestioned benefit must result from administering thyroid. Should the first three diagnostic requirements be met, one can with certainty predict a change of these criteria toward normal following the administration of thyroid therapy.

Classification of Hypothyroidism

- (1) Cretinism with thyroid deficiency
- (2) Childhood myxedema (spontaneous)
- (3) Adult myxedema (spontaneous)
- (4) Post thyroiditis myxedema
- (5) Postoperative myxedema

Cretinism with Thyroid Deficiency

Early recognition is essential for the successful treatment of cretinism since even adequate treatment when given late produces disappointing results. Therefore, therapy should be started within the first months of life during which time the important brain centers are undergoing development. A maintenance dose of USP thyroid which will establish normal body growth should be given. During the first 4 months of life, $\frac{1}{2}$ gram, during the second 4 months $\frac{3}{8}$ gram, and from 8 months to 12 months, $\frac{1}{2}$

the patient reaches the age of twelve at which time the dose = 1 gram daily. After sixteen years of age the daily maintenance dose should be 1½ grams. When embarking on treatment for established cretinism the family must be advised that thyroid is a requirement for normal body growth and that under no circumstance should treatment be altered or discontinued. A schedule of dosage should be carefully outlined with instructions regarding the type of thyroid to be given, and a prescription for the thyroid written in duplicate, permitting the druggist to refill it when necessary. Failure to instruct

the family properly regarding future treatment leads to poor management which results in faulty physical and mental development.

Should cretinism be discovered late in childhood, the initial dose of thyroid should be twice the suggested dose for that age. A large dose of thyroid is given in the hope of forcing growth at a rate more rapid than normal. One should not, however, expect complete restoration to normal when treatment is started late. Should a cretin reach adult life without receiving thyroid, no improvement in mentality or growth will result from therapy.

At or shortly after birth, congenital cretins are occasionally noted to have adenomatous goiters. These goiters may alter the clinical course of the thyroid deficiency since as they increase in size there is gradual production of thyroid hormone which leads to lessening of thyroid deficiency. Clinical improvement may continue until euthyroidism results, should excess thyroid hormone be produced, typical hyperthyroidism results. This improvement in thyroid deficiency which may occur in cretins with goiters necessitates gradual reduction of the maintenance dose of thyroid. Should hyperthyroidism actually develop, thyroidectomy is necessary. After thyroidectomy, careful observation must be continued since thyroid deficiency may again develop so that administration of supplementary thyroid again becomes necessary.

Childhood Spontaneous Myxedema. Children who are normal at birth, grow and develop normally, and then become thyroid deficient are considered to have childhood myxedema. The diagnosis of this condition is frequently delayed since the pallor, edema of the face, and retarded growth are frequently thought to be caused by anemia or renal disease. The absence of demonstrable renal disease, the presence of an elevated blood cholesterol, and roentgenologic evidence of retarded bone age aid in confirming the diagnosis of thyroid deficiency.

The treatment of these children with thyroid results in prompt improvement in the

normal level. Between the ages

years, USP thyroid in a dose of $\frac{1}{2}$ gram usually suffices as does $\frac{1}{4}$ gram from the age of 4 to 12 years. The dose of thyroid may be safely increased by an additional $\frac{1}{4}$ gram in an attempt to incite a slightly more rapid bone growth than normal so that the patient may recover that which was lost during the period of thyroid deficiency. In addition to the blood cholesterol level another excellent guide to the therapeutic response is the change noted in the bone age as determined by comparative roentgenograms of the hands. Basal metabolic rates are rarely necessary for judging therapeutic response. Continued observation of these children is advisable so that the dose of thyroid may be altered with increase in age. Here also the family should be acquainted with the future need for treatment with thyroid to obtain proper mental and physical development.

Adult Spontaneous Myxedema The treatment of myxedema in adults should be divided into the management of patients less than 45 or 50 years and of those over 50 years of age. This division according to age is extremely important since patients in the older age group must be given cautious treatment if serious cardiac complications are to be avoided. The younger patients tolerate sizable doses of thyroid with safety and many standard textbooks advise starting treatment of all patients who have myxedema with doses as large as 3 grains daily. Even in the younger patients this dose seems in excess and it is preferable for the initial dose to be only $\frac{1}{2}$ gram daily. After 6 weeks to 2 months of treatment on this dosage ($\frac{1}{2}$ gram daily) the patient should be studied again and a decision reached as to the future maintenance dose. In most instances 1 gram of thyroid daily restores the patient to good health, with the basal metabolic rate and blood cholesterol level returning to normal. A daily dose of USP thyroid in excess of 1 $\frac{1}{2}$ grains is never necessary to accomplish satisfactory euthyroidism.

Older patients with spontaneous myxedema require cautious administration of thyroid. These patients frequently have associated heart disease and many have had long standing myxedema which leads to hypercholesterolemia with resulting coronary sclerosis. Therefore, they must be given only a small initial dose of thyroid and the longer

the duration of myxedema, the smaller the initial dose. Should the patient have symptoms of angina, extreme caution will be necessary. The initial dose of thyroid in the older patients should never be over $\frac{1}{2}$ gram daily and should the patient have suggestive cardiac symptoms it should not exceed $\frac{1}{10}$ gram a day.

Older patients must be carefully observed and advised that if any cardiac symptoms develop or if those present become aggravated, the administration of thyroid must be discontinued and started again in smaller doses. If at the end of one month the initial dose of thyroid is tolerated, it may then be slowly increased. Monthly observations are continued until an adequate maintenance dose of thyroid is reached, which should rarely exceed 1 gram a day. Many patients tolerate only a small dose of thyroid because of troublesome angina when larger doses are given. The clinical improvement, however, from a dose of thyroid as small as $\frac{1}{10}$ gram a day is at times considerable. Angina may improve following the institution of thyroid treatment but this is not common. Should it occur, the dose of thyroid may be cautiously increased.

Post thyroiditis Myxedema Seven per cent of medical cases with thyroiditis and 50 per cent of patients with thyroiditis which required surgery developed myxedema.

dose of thyroid required for satisfactory control is usually small, varying from $\frac{1}{2}$ to 1 gram a day. The dose must, however, be individualized and an attempt made to accomplish control as determined by the patient's symptoms, the basal metabolic rate and the level of the blood cholesterol. Caution must be followed in treating older patients.

Postoperative Myxedema Myxedema follows subtotal thyroidectomy in approximately 25 per cent of cases. Should microscopic study of the removed thyroid tissue show strumitis, the likelihood of myxedema developing is increased so that careful observation during a 3 to 6 month postoperative period is advisable. Postoperative myxedema may at times be so transient that treatment is not indicated, but if it continues

beyond a 3 month period, therapy becomes necessary. If treatment becomes necessary, it does not follow that it must be continued indefinitely, therefore, treatment should be withdrawn after a period of 6 to 9 months to determine with certainty if it is necessary. The dose of thyroid should be the smallest possible to accomplish full control, and older patients should be cautiously treated.

ELMER C BARTELS

REFERENCES

- Bartels, E C. Profound Myxedema with Normal Plasma Cholesterol. *Lahey Clin Bull*, 5:187, 1947.
- Bartels, E C. Hyperthyroidism Developing in Cretin. *S Clin North America*, 25:672, 1945.
- Bartels, E C., and Bell G. Myxedema and Coronary Sclerotic Heart Disease. *Tr Am A Study of Goiter*, 1939, abs in *Lahey Clin Bull*, 1:21, 1939.
- Marshall S F, Meissner W A and Smith D C. Chronic Thyroiditis. *New England J Med* 238:758, 1948.

THYROIDITIS

The treatment of thyroiditis is determined by an understanding of the nature of the pathologic process which is involving the thyroid gland. Therefore, before instituting any type of therapy consideration should be given to determining the basis of the thyroid involvement. Many times this knowledge can be obtained only by biopsy study or culture, which procedure may be combined with specific therapeutic or ameliorative measures.

Acute Thyroiditis. Acute thyroiditis may be nonsuppurative or suppurative with definite abscess formation. Any one of a large number of organisms may be responsible for this condition. Among these are such bacteria as the streptococcus, staphylococcus, pneumococcus, *Bacillus coli*, or anaerobic organisms, and even virus infections are probably responsible at times.

This acute type of thyroid involvement is treated symptomatically by the local application of cold compresses or ice packs, and aspirin, 0.6 gm, or codeine, 30 mg, is given for relief of pain. Trial treatment with antibiotic drugs, sulfonamides, penicillin, or streptomycin, given singly or in combination, should be carried out. Should the specific offending organism be known, more intelligent antibiotic therapy can be used. Should

calization of the abscess or infection to one lobe.

Thiouracil has been reported as being beneficial for the treatment of acute thyroiditis. The first report, by King and Rosellum, indicated that 8 of 11 patients were promptly cured. In all 8 patients the process was 3 weeks or less in duration and all were symptom free in one week, with complete disappearance of the thyroid enlargement. Three patients did not respond to the drug. The 2 cases reported by Cantwell obtained benefit in 48 hours. One of the 2 patients did not respond to treatment with penicillin and sulfadiazine. Thiouracil was administered in a daily dose of 600 mg, 200 mg three times a day. That thiouracil is not specific for acute thyroiditis is indicated by personal experience with 2 patients who had identical thyroiditis, one responded promptly and in one patient the disease ran its usual course, starting in one lobe and proceeding to the other lobe in spite of continuous thiouracil treatment. At the 1948 meeting of the American Goiter Association in Toronto Dr King reported continued success with the use of thiouracil in thyroiditis, however, similar results did not follow the use of propylthiouracil.

Chronic Thyroiditis. Chronic thyroiditis includes those conditions which the pathologists have differentiated as nonspecific thyroiditis, Riedel's struma, Hashimoto's struma, infectious granuloma, which includes syphilis, and tuberculosis and amyloidosis of the thyroid. The first three types of thyroiditis include most of the cases of thyroiditis with Hashimoto's struma making up 40 per cent of cases, nonspecific thyroiditis 35 per cent, and Riedel's struma 25 per cent. Although the diagnosis of chronic thyroiditis can be made with reasonable certainty, it must be differentiated from carcinoma. Therefore, biopsy is indicated in any case in which there is any possible doubt as to the diagnosis. That the diagnosis of thyroiditis is not considered sufficiently often is indicated by a recent report (Marshall). Of 187 cases of thyroiditis proved by biopsy, the correct diagnosis was considered preoperatively in only 25 per cent of the cases.

Many patients with chronic thyroiditis do not require any type of treatment, but should pressure symptoms develop the choice of therapy is surgery. In addition to securing definite information as to the pathologic process in the thyroid gland, relief of pressure on the trachea is accomplished by removing a wedge shaped piece of thyroid which should include the isthmus and medial portions of the lobes overlying the trachea. The prethyroid muscles are then sutured to the tracheal fascia to prevent the thyroid lobes from becoming adherent to each other with return of pressure on the trachea. In nonspecific thyroiditis this procedure may be all that is necessary, however, in Riedel's struma, in which the thyroid is adherent to all the surrounding structures there may be sufficient edema and even involvement of the recurrent nerve to make tracheotomy necessary. Only the smallest amount of thyroid tissue necessary to relieve tracheal obstruction should be removed so as to avoid injury to the recurrent laryngeal nerves, injury to or removal of parathyroid glands, or an increased incidence of myxedema. Even so postoperative myxedema, requiring treatment develops in 80 per cent of patients with thyroiditis who undergo conservative surgical procedures on the thyroid gland. Should myxedema develop maintenance treatment with desiccated thyroid is indicated, using doses of thyroid adequate to return the basal metabolic rate and cholesterol level to normal. In most patients who develop myxedema desiccated thyroid must be taken indefinitely. Tetany is a rare development.

Röntgen irradiation of the thyroid has been suggested for the treatment of thyroiditis and some favorable results are reported in the literature. The additional fibrosis resulting from the reaction of irradiation may increase the constriction on the trachea and also further destroy remaining normal thyroid tissue, leading to myxedema.

Tuberculous thyroiditis which is extremely rare can be diagnosed only by biopsy and pathologically it is usually of the miliary type. Satisfactory results usually result from roentgen therapy.

Luetic thyroiditis, which is also rare, may occur during secondary syphilitic manifestations or may be gummatous in nature. The diagnosis is usually made by biopsy. Anti-

syphilitic treatment results in prompt disappearance of the thyroid enlargement.

ELMER C BARTELS

REFERENCES

- Cantwell, R. C. Thiouracil in Acute Thyroiditis. *Ann. Int. Med.*, 29:736, 1948.
 Ling, B. T., and Rosellini, L. J. Treatment of Acute Thyroiditis with Thiouracil. *J. A. M. A.*, 129:267, 1945.
 Marshall, S. F., Meissner, W. A., and Smith, D. C. Chronic Thyroiditis. *New England J. Med.*, 239:758, 1948.

THE PARATHYROID GLANDS

The parathyroid glands are subject to a variety of diseases which usually produce some alteration in the function of the glands. Regardless of whether hyperfunction or hypofunction follows the pathologic process, the disturbances in calcium and phosphorus metabolism which accompany the change in function play a dominant role in producing symptoms and in determining treatment.

Hypoparathyroidism. **PHYSIOLOGIC CONSIDERATIONS.** Hypoparathyroidism is most commonly caused by the accidental removal of the parathyroid glands or interference with their blood supply during operation on the thyroid. It may also follow removal of a parathyroid adenoma. More rarely, it occurs spontaneously as a chronic idiopathic variety without known cause. Monodiasis has been associated with some of the spontaneous cases and has been considered as a possible etiologic factor. Other reported causes include acute infections such as measles and influenza, chronic inflammatory changes such as tuberculosis and syphilis, and radiation injury.

Parathyroid insufficiency which follows surgery on the thyroid or parathyroid glands usually occurs within 24 to 48 hours after the operation. The onset is acute and the symptoms consist of excitability, anxiety, numbness and paresthesias of the lips and hands, carpopedal spasm, occasionally laryngeal spasm, and sometimes convulsions. In some individuals the symptoms are so severe as to demand immediate and effective treatment. In contrast to this, chronic parathyroid insufficiency has an insidious onset and may exist for a long time before it is recognized. It produces a variety of symptoms including

paresthesias, mental depression, periodic attacks of tetany with or without convulsions, and finally cataracts and trophic changes in the nails and hair

tion in the amount of circulating parathyroid hormone. The lack of the hormone produces a fall in the calcium content of the blood serum, a decrease in the urinary excretion of phosphates and calcium, and an accumulation of phosphate in the blood serum, in addition, it causes a decrease in the normal activity of the osteoclasts. The serum calcium usually falls below 7 mg. per 100 cc., and the serum phosphorus rises to 5 or 6 mg. per 100 cc., although in some cases it has increased to as much as 16 mg. per 100 cc. The low serum calcium content is responsible for the increased neuromuscular excitability, tetany, cataracts, and trophic changes. The diagnosis of hypoparathyroidism is confirmed by the presence of a low serum calcium, a high serum phosphorus, and absence of, or greatly decreased, calcium in the urine in association with signs of tetany. Renal insufficiency should be excluded since it may be responsible for changes in the levels of serum calcium and phosphorus which are similar to those of parathyroid insufficiency.

The treatment of hypoparathyroidism has as its goal the relief of symptoms and the restoration of serum calcium to normal levels. Inadequate treatment and its associated subnormal serum calcium levels may eventually be followed by the development of cata-

not completely controlled by the use of calcium and vitamin D or dihydrotachysterol. The use of parathyroid hormone is rarely necessary except in the treatment of acute tetany where it is highly effective. The choice of medication is dependent on the acuteness and severity of the parathyroid insufficiency as well as the individual variation in the response to each medication.

ACUTE HYPOPARATHYROIDISM The treatment of acute hypoparathyroid tetany consists mainly in the administration of large doses of calcium orally, supplemented by

occasional parenteral injections. Treatment is initiated by the intravenous administration of 10 to 20 cc. of a 10 per cent solution of calcium gluconate. This may be repeated at intervals of every few hours if needed. In severe tetany a constant intravenous drip of calcium gluconate may be used. This preparation may also be given intramuscularly if necessary. Calcium chloride (5 per cent solution) may be used in place of calcium gluconate and in the same dose. It must never be given intramuscularly, and great care must be used to avoid any spillage outside the vein since such extravasation will produce a slough. Furthermore, venous thrombosis at the site of the injection sometimes follows its use. All calcium preparations given intravenously should be injected slowly to avoid unpleasant flushing, nausea, vomiting and fall in blood pressure.

ing the calcium in the powdered form has proved to be satisfactory and is usually well tolerated by the patient. It is administered in doses of 4 gm. every 2 hours until numbness and tingling have subsided. Each 4 gm. dose is dissolved in hot water and then flavored with some palatable liquid. Canned orange juice is satisfactory, although other fruit juices, tomato juice, or tea may be substituted. When the acute symptoms of tetany have been relieved, the patient is placed on a maintenance dose of calcium lactate of 1 or 2 heaping teaspoonsful (4 to 8 gm.) three or four times a day. Calcium chloride, which may be substituted for calcium lactate, is readily soluble in water, provides a high percentage of available calcium, and is well absorbed from the gastrointestinal tract. Its chief drawbacks are its astringent action in the mouth and

juice

The chief indication for the use of parathyroid hormone is in the treatment of those patients with acute tetany who cannot take sufficient calcium by mouth, either because of inability to swallow or because of nausea and vomiting. The patient over the critical

take an adequate dosage of calcium and vitamin D or dihydrotachysterol orally Parathyroid hormone causes a lowering of the serum phosphorus level by producing a phosphate diuresis, and an increase in the serum calcium level by stimulation of the osteoclasts The maximal effect of parathyroid hormone is reached in 8 to 24 hours, with a peak at about 15 hours It is given initially in a dose of 50 to 100 units intramuscularly and repeated in 12 hours if necessary Thereafter 10 to 20 units may be given daily until treatment with calcium and an activated sterol becomes effective Frequent determinations of the serum calcium level should be made in order to control the dose properly Prolonged treatment with the hormone is unnecessary since other measures are completely successful in controlling even severe cases In addition, frequent injections over a long period might lead to the development of antihormones which necessitate the administration of larger and larger doses in order that the desired effects may be achieved

Additional measures are sometimes necessary in the treatment of acute tetany The intake of milk in the diet should be restricted because of its high phosphate content A high intake of phosphate is capable of precipitating tetany, for with a rise in the serum phosphorus level the serum calcium level may be further depressed, thus favoring the appearance of tetany (Jones)

Severe laryngeal spasm in rare cases may require laryngeal intubation or even tracheotomy Paralysis of one vocal cord in association with tetany predisposes to the development of laryngeal spasm

CHRONIC HYPOPARATHYROIDISM The severity of the tetany and its response to calcium therapy will indicate the degree of parathyroid insufficiency and the need for further treatment Tetany which follows thyroid surgery may disappear spontaneously within a few days as the edema in the tissues of the neck subsides or within 2 or 3 months as the remaining parathyroid glands hypertrophy More rarely, it is permanent, requiring prolonged maintenance treatment Mild cases of tetany are sometimes fully controlled by calcium therapy alone More often the use of calcium in combination with one of the activated sterols is necessary

Calcium lactate is administered orally in doses of 1 or 2 heaping teaspoonfuls three or four times daily The total daily dose may be prepared each morning and divided into four or five equal portions to be taken at properly spaced intervals through the day To facilitate absorption from the gastro-intestinal tract, each dose should be taken before meals

The activated sterols play an important role in the management of chronic parathyroid insufficiency (McLean). Calciferol (vitamin D₂) and dihydrotachysterol (A T 10) are two irradiation products of ergosterol which possess the same actions of increasing

excretion than on calcium absorption Its action resembles that of parathyroid hormone more closely than does the action of vitamin D and for this reason would seem to be the ideal drug Vitamin D has a greater effect on calcium absorption than on phosphate excretion It has a slower action than A T 10 but its effect on the serum calcium level is more prolonged The results of treatment with vitamin D have been highly satisfactory Since it is less expensive than A T 10, it is usually prescribed first

Calciferol (vitamin D₂) is available in pure crystalline form and is dispensed in capsules containing 50,000 international units each One milligram of calciferol is equivalent to 40,000 international units Di-

in capsules each containing 0.625 mg of the crystalline sterol and 2 capsules are equivalent to 1 cc On the basis of comparative studies both in animals and human beings, 1 cc of dihydrotachysterol (containing 1.25 mg of the crystalline substance) is equivalent to about 10 mg of calciferol or 400,000 international units

The plan of treatment with the activated sterols is to give large initial doses until the serum calcium is near the normal level and then to reduce it to small daily maintenance doses The initial dose of dihydrotachysterol is 2 to 3 cc (4 to 6 capsules) per day until the serum calcium is normal It is then re-

duced to about 2 to 5 cc per week. A corresponding initial dose of calciferol would be 800,000 to 1,200,000 units daily, however, it is rarely necessary to give as large an amount as this since adequate effect usually can be obtained with 300,000 to 800,000 units daily. The maintenance dose of calciferol varies between 50,000 and 200,000 units per day. Calcium should always be given with the activated sterols.

Treatment is controlled by observing the patient's response by periodic determinations of serum calcium and occasionally by the use of the urinary Sulkowitch test. In sufficient treatment is associated with such

steroids is quite quickly apparent to the patient because of headache, nausea, vomiting, and an intense dislike or aversion to calcium (Hurxthal and Claiborne). Medication is often discontinued by the patient himself be-

of these reactions. In contrast patients with conditions other than tetany who are receiving a high dosage of vitamin D may experience prolonged intoxication without being aware of it. It is in such cases that kidney damage and metastatic calcification are most likely to occur.

Periodic determinations of the serum calcium provide the most reliable control of therapy. The urinary Sulkowitch test has been recommended (Albright et al.) also as a guide to treatment. The test is a rough quantitative measure of the urinary excretion of calcium. It is performed by adding 5 cc of urine to 5 cc of Sulkowitch reagent. If no precipitate is formed the urine is free of calcium and the serum calcium is below the renal threshold of about 7.5 mg. per 100 cc. If a fine precipitate is formed the serum calcium is between 8 and 10 mg. per 100 cc. A heavy white cloud indicates a serum calcium level above 11 mg. per 100 cc. The test has its greatest usefulness during the initial treatment of tetany before the serum calcium has reached normal levels. A negative Sulkowitch test indicates that the dosage of activated sterol is inadequate. When the

test becomes consistently positive it is safer to rely on serum calcium determinations.

Supplementary measures may be prescribed but are only rarely necessary. Low phosphate diets have been recommended on sound theoretical grounds, but are difficult to follow. Restriction of the intake of milk is advisable in all cases. The use of amphotel (120 to 160 mc. per day) has been advocated as a means of reducing the absorption of phosphates from the intestinal tract, but this is usually unnecessary. Acidifying salts such as ammonium chloride may be useful for the treatment of tetany resulting from alkalosis, but they have no place in the management of hypoparathyroidism. Desiccated thyroid should be prescribed only if an associated thyroid deficiency is present. It may be of incidental help in the mobilization of calcium but this is of minor importance and not an indication for its use.

With proper management, patients with hypoparathyroidism can be kept in a perfectly normal physical and chemical state. If cataracts have already formed prior to the institution of treatment, the maintenance of a normal blood calcium inhibits their further growth but will not cause them to disappear. Careful supervision of the patient, however, is necessary in order to secure the best results.

Primary Hyperparathyroidism Primary hyperparathyroidism is a condition resulting from excessive production of the parathyroid hormone, which in turn causes marked changes in the metabolism of calcium and phosphorus. Most of the cases (86 per cent) are caused by a hyperfunctioning parathyroid adenoma, and about 14 per cent of cases

pal actions that of increasing the urinary excretion of phosphorus, and that of increasing the activity of the osteoclasts. As a result, there is a decrease in the level of serum phosphorus, an increase in the level of serum calcium, an increase in the urinary excretion of calcium and phosphorus, and demineralization of bones.

The symptoms are the result of these physiologic changes. Hypercalcemia is responsible for muscular weakness and atony, constipation, loss of appetite, loss of weight,

take an adequate dosage of calcium and vitamin D or dihydrotachysterol orally. Parathyroid hormone causes a lowering of the serum phosphorus level by producing a phosphate diuresis and an increase in the serum calcium level by stimulation of the osteoclasts. The maximal effect of parathyroid hormone is reached in 8 to 24 hours with a peak at about 15 hours. It is given initially in a dose of 50 to 100 units intramuscularly and repeated in 12 hours if necessary. Thereafter 10 to 20 units may be given daily until treatment with calcium and an activated sterol becomes effective. Frequent determinations of the serum calcium level should be made in order to control the dose properly. Prolonged treatment with the hormone is unnecessary since other measures are completely successful in controlling even severe cases. In addition frequent injections over a long period might lead to the development of antihormones which necessitate the administration of larger and larger doses in order that the desired effects may be achieved.

Additional measures are sometimes necessary in the treatment of acute tetany. The intake of milk in the diet should be restricted because of its high phosphate content. A high intake of phosphate is capable of precipitating tetany for with a rise in the serum phosphorus level the serum calcium level may be further depressed thus favoring the appearance of tetany (Jones).

Severe laryngeal spasm in rare cases may require laryngeal intubation or even tracheotomy. Paralysis of one vocal cord in association with tetany predisposes to the development of laryngeal spasm.

CHRONIC HYPOPARATHYROIDISM The severity of the tetany and its response to calcium therapy will indicate the degree of parathyroid insufficiency and the need for further treatment. Tetany which follows thyroid surgery may disappear spontaneously within a few days as the edema in the tissues of the neck subsides or within 2 or 3 months as the remaining parathyroid glands hypertrophy. More rarely it is permanent requiring prolonged maintenance treatment. Mild cases of tetany are sometimes fully controlled by calcium therapy alone. More often the use of calcium in combination with one of the activated sterols is necessary.

Calcium lactate is administered orally in doses of 1 or 2 heaping teaspoonfuls three or four times daily. The total daily dose may be prepared each morning and divided into four or five equal portions to be taken at properly spaced intervals through the day. To facilitate absorption from the gastrointestinal tract each dose should be taken before meals.

The activated sterols play an important role in the management of chronic parathyroid insufficiency (McLean). Calciferol (vitamin D₂) and dihydrotachysterol (AT 10) are two irradiation products of ergosterol which possess the same actions of increasing

tachysterol has a greater effect on phosphate excretion than on calcium absorption. Its action resembles that of parathyroid hormone more closely than does the action of vitamin D and for this reason would seem to be the ideal drug. Vitamin D has a greater effect on calcium absorption than on phosphate excretion. It has a slower action than AT 10 but its effect on the serum calcium level is more prolonged. The results of treatment with vitamin D have been highly satisfactory. Since it is less expensive than AT 10 it is usually prescribed first.

Calciferol (vitamin D₂) is available in pure crystalline form and is dispensed in capsules containing 50 000 international units each. One milligram of calciferol is equivalent to 40 000 international units. Di

crystalline sterol and 2 capsules are equivalent to 1 cc. On the basis of comparative studies both in animals and human beings 1 cc of dihydrotachysterol (containing 125 mg of the crystalline substance) is equivalent to about 10 mg of calciferol or 400 000 international units.

The plan of treatment with the activated sterols is to give large initial doses until the serum calcium is near the normal level and then to reduce it to small daily maintenance doses. The initial dose of dihydrotachysterol is 2 to 3 cc (4 to 6 capsules) per day until the serum calcium is normal. It is then re-

duced to about 2 to 5 cc per week. A corresponding initial dose of calciferol would be 800 000 to 1 200 000 units daily; however it is rarely necessary to give as large an amount as this since adequate effect usually can be obtained with 300 000 to 800 000 units daily. The maintenance dose of calciferol varies between 50 000 and 200 000 units per day. Calcium should always be given with the activated sterols.

Treatment is controlled by observing the patient's response by periodic determinations of serum calcium and occasionally by the use of the urinary Sulkowitch test. In sufficient treatment is associated with such symptoms as anxiety, irritability, mental depression and paresthesias of lips and fingers. Chvostek's and Trousseau's signs can usually be elicited. Overdosage with the activated sterols is quite quickly apparent to the patient because of headache, nausea, vomiting and an intense dislike or aversion to calcium (Hurxthal and Claiborne). Medication is often discontinued by the patient himself because of the gastro-intestinal symptoms. Prolonged intoxication from the activated sterols is not likely in patients with tetany because of these reactions. In contrast, patients with conditions other than tetany who are receiving a high dosage of vitamin D may experience prolonged intoxication without being aware of it. It is in such cases that kidney damage and metastatic calcification are most likely to occur.

Periodic determinations of the serum calcium provide the most reliable control of therapy. The urinary Sulkowitch test has been recommended (Albright et al.) also as a guide to treatment. The test is a rough quantitative measure of the urinary excretion of calcium. It is performed by adding 5 cc of urine to 5 cc of Sulkowitch reagent. If no precipitate is formed the urine is free of calcium and the serum calcium is below the renal threshold of about 7.5 mg per 100 cc. If a fine precipitate is formed the serum calcium is between 8 and 10 mg per 100 cc. A heavy white cloud indicates a serum calcium level above 11 mg per 100 cc. The test has its greatest usefulness during the initial treatment of tetany before the serum calcium has reached normal levels. A negative Sulkowitch test indicates that the dosage of activated sterol is inadequate. When the

test becomes consistently positive it is safer to rely on serum calcium determinations.

Supplementary measures may be prescribed but are only rarely necessary. Low phosphate diets have been recommended on sound theoretical grounds but are difficult to follow. Restriction of the intake of milk is advisable in all cases. The use of amphotel (120 to 160 cc per day) has been advocated as a means of reducing the absorption of

thyroid deficiency is present. It may be of incidental help in the mobilization of calcium but this is of minor importance and not an indication for its use.

With proper management patients with hypoparathyroidism can be kept in a perfectly normal physical and chemical state. If cataracts have already formed prior to the institution of treatment the maintenance of a normal blood calcium inhibits their further growth but will not cause them to disappear. Careful supervision of the patient however is necessary in order to secure the best results.

hormone which in turn causes marked changes in the metabolism of calcium and phosphorus. Most of the cases (86 per cent) are caused by a hyperfunctioning parathyroid adenoma and about 14 per cent of cases are the result of hyperplasia or hypertrophy of all four parathyroid glands.

The parathyroid hormone has two principal actions: that of increasing the urinary excretion of phosphorus and that of increasing the activity of the osteoclasts. As a result there is a decrease in the level of serum phosphorus, an increase in the level of serum calcium, an increase in the urinary excretion of calcium and phosphorus and demineralization of bones.

The symptoms are the result of these physiologic changes. Hypercalcemia is responsible for muscular weakness and atony, constipation, loss of appetite, loss of weight

and cardiac irregularities. The hypercalcaemia produces polyuria, haematuria, renal or ureteral colic and diminished renal function. The increased activity of the osteoclasts leads to a generalized decalcification of bones with cyst formation. The pathologic changes in the kidneys are of major importance since the ultimate prognosis in any given case is dependent on the extent and severity of the renal damage. Renal calculi or calcification occurs in 92 per cent of the cases whereas bone changes are present in only 67 per cent of cases (Keating and Cook). The longer the disease exists the greater is the damage to the kidneys and once the damage is sufficiently marked recovery of renal function will not take place. Therefore early diagnosis and proper treatment are of the utmost importance (Lacey).

The only treatment is surgical removal of the offending adenoma or subtotal resection of all four hyperplastic parathyroid glands. The diagnosis of primary hyperparathyroidism should of course be firmly established before parathyroid surgery is undertaken. The difficulties encountered by the surgeon in locating the adenoma are at times so great that unless the diagnosis is positive the operation may be discontinued short of finding the tumor.

Following the operation a state of hypoparathyroidism may develop which demands medical therapy. A preoperative serum alkaline phosphatase above 20 Bodansky units and the existence of renal damage are two indicators of the likelihood of postoperative tetany. Tetany which occurs as a result of the removal of too much parathyroid tissue is treated in the same manner as tetany which follows goiter surgery. Tetany which occurs in the presence of marked skeletal decalcification and increased activity of the osteoblasts (serum phosphatase above 20

Bodansky units) is likely to be severe (Churchill and Cope). The increased demand of the bones for lime salts results in marked lowering of the serum calcium and the serum phosphorus tends to remain low or may even decrease. These changes in serum calcium and phosphorus tend to persist until excessive osteoblastic activity ceases and serum phosphatase returns to a normal level at which time parathyroid function reaches normal. The treatment of this type of tetany requires a large intake of dietary calcium and in the acute phase frequent intravenous calcium injections may be necessary. There are theoretical objections to the use of parathyroid hormone and the activated sterols but nevertheless these may occasionally be used. Vitamin D with its greatest action on calcium absorption would seem to be the most desirable.

GEORGE O BELL

REFERENCES

- Albright F: Note on Management of Hypoparathyroidism with Dihydrotachysterol. *JAMA* 112:2592, 1939.
 Albright F et al: Comparison of Effects of AT 10 (Dihydrotachysterol) and Vitamin D on Calcium and Phosphorus Metabolism in Hypoparathyroidism. *J Clin Invest* 17:317, 1939.
 Keating F C et al: A New Chemical Treatment

ke

La

- to dism Lacey Can But 400 1941
 McLean F C: Activated Sterols in the Treatment of Parathyroid Insufficiency. Review. *JAMA* 117:609, 1941.

OVARIAN DISEASES

AMENORRHEA AND HYPOMENORRHEA

Amenorrhea and hypomenorrhea are symptoms rather than disease entities and for this reason treatment should be directed toward the factors producing the menstrual failure. But the problem is not simple. Al-

though our knowledge of menstrual physiology is far more complete than it was a few years ago nevertheless there are many complex endocrine interrelationships which are either entirely unknown or being known cannot be regulated.

In any case of amenorrhea irrespective of

whether primary (the patient being more than 17 years of age and having never menstruated) or secondary (cessation of menstruation after it is once established) there are two considerations which are of primary importance and must be investigated before any specific therapy is undertaken. First, it must be determined whether there is any gross abnormality of the pelvic structures. Vaginal examination is infinitely preferable to rectal examination for this purpose and should be done whenever it is at all feasible. In the vaginal patient, employing copious amounts of lubricant and using the utmost gentleness, it is generally possible to make a satisfactory one finger vaginal examination and to visualize the cervix. Any pelvic abnormalities which are found should be dealt with on their own merits. Second, a general evaluation of the patient should be made. This will include (1) notation of habitus, development of secondary sex characteristics, etc., which may suggest pituitary disease, ovarian agenesis or the like, (2) a detailed physical examination. The minimal laboratory studies which should be done are a complete blood count, urinalysis, basal metabolism and roentgen examination of the chest. The course after this information is assembled will depend in large measure on any abnormalities which are found. Deviations in habitus or development which are considered as endocrine in origin (pituitary, ovarian, or adrenal) are best left for later consideration. The immediate effort should be the improvement of the patient's general health. Specific advice is given concerning diet, rest, the avoidance of excesses and exercise out of doors according to the patient's tolerance or inclination. Anemia, which is a common finding, should be corrected. (Except in the anemias specifically requiring liver therapy, it is unusual to find a patient in whom iron by mouth in one form or another is not promptly effective and well tolerated.) If the basal metabolism is low, thyroid should be given in doses which will elevate the rate to normal or slightly above normal. In fact, of all therapy available for the treatment of amenorrhea, thyroid extract is by far the most useful. In many cases where the MMR is normal to start with, periodic menstruation is initiated by giving small doses of thyroid to the point

In a significant percentage of cases the measures outlined above will be effective in establishing menstruation. If they are not, it must be decided whether or not specific endocrine therapy is warranted, and this decision must by all means be deferred until

grandmothers can be made to bleed at will by substitution therapy, but this bleeding serves no useful purpose. So it is in amenorrhea, the mere production of uterine bleeding can hardly be considered a therapeutic triumph, unless the therapy causing the bleeding at the same time effects some improvement in the condition which causes the symptom.

In primary amenorrhea, it is agreed that no specific attempt should be made to initiate menstruation before the age of 17 because of the frequency with which late puberty may occur up to this time. Actually, of course, such individuals need no therapy and if left alone will menstruate spontaneously.

Thyroid therapy is stopped, nor is this bleeding associated with ovulation, since it is of the "estrogen withdrawal" type. Occasional reports indicate that such cyclic therapy is occasionally followed by ovulation and growth of the hypoplastic uterus, and that true menstruation becomes established. Certainly such cases are rare. I have seen one patient with complete agenesis of the ovaries in whom hysterectomy was necessary to control the uterine hemorrhage which resulted from attempts to establish menstruation by the use of estrogens. As a rule, the treatment of primary amenorrhea should be limited to the routine general measures which were outlined above. If one expressly sets out to produce uterine bleeding by substitution therapy, he should do so only with the knowledge that in all probability it will serve no useful purpose except for its dubious psychologic value, and that periodic men-

stration will be unlikely unless the therapy is continued indefinitely

In secondary amenorrheas, cyclic therapy with estrogens or progesterone or both may have some occasional use, since periodic menstruation may sometimes continue after the therapy is stopped. But it is emphasized that such therapy should be carried on only by one who is thoroughly familiar with the physiology of menstruation, and who is capable of appraising the results he is achieving. The important indication for specific therapy is the patient with secondary amenorrhea who complains also of sterility. Several regimens have been outlined, all of them having entirely unpredictable and doubtful value. Stilbestrol (0.5 to 1.0 mg.) or its equivalent may be given nightly for 2 weeks, uterine bleeding will follow in about one week, after which the course may be repeated for two or three periods. Some have advocated various combinations of progesterone and estrogen, though it is doubtful that these are any more effective in producing ovulation than the estrogens alone. Gonadotropic hormones are generally agreed to be ineffective. Roentgen therapy in small doses to the pituitary and ovaries has recently been advocated. However, geneticists have shown serious gene mutations in later

should not be lightly undertaken in the human being

DAVID N. DANFORTH

REFERENCE

Novak E. *Textbook of Gynecology*. Ed. 3. Baltimore: Williams & Wilkins Company, 1948. p. 570.

MENORRHAGIA AND METRORRHAGIA

Menorrhagia refers to abnormally profuse or abnormally prolonged menstruation. Metrorrhagia refers to bleeding between the periods, and generally is accompanied by menorrhagia. Both of these symptoms may have extremely serious implications, and deserve the most meticulous gynecologic study. They may result from various pathologic lesions of the reproductive tract, or they may

be functional in nature, resulting from known or indeterminate endocrine causes. The listing of these possibilities and their therapy is inappropriate in this volume. Suffice it to say that, irrespective of the patient's age, it is improper to consider excessive bleeding as functional in nature until curettage has eliminated the possibility of malignancy. In younger women this dictum will subject many patients to what may appear to be needless curettage. But even if the bleeding is purely functional, curettage is frequently followed by marked if often temporary, relief. Furthermore, in adolescent patients it is sometimes impossible to make an adequate vaginal examination except under anesthesia, the anesthesia employed for curettage affords opportunity for easy palpation of the adnexa and detection of any pelvic masses which may be related to the bleeding.

In addition to curettage and an adequate vaginal examination, there are other determinations which must be made before specific therapy is employed. First an evaluation of the patient's general health and physical condition must be made, and any deficiencies corrected. If bleeding has been heavy, anemia will almost certainly be present and must be treated. This responds well to ferrous sulfate—2 gm. t.i.d.—and does not require the more expensive combinations of iron with liver and the like, nor is parenteral liver therapy indicated. Occasionally, blood dyscrasias may account for menorrhagia, for this reason the bleeding time, platelet count and clot retraction must be tested. Also a basal metabolic rate should be taken, since menorrhagia may accompany either hypothyroid or hyperthyroid states, and will usually respond to the correction of this abnormality.

If the above investigation has shown no abnormality which might account for the bleeding, and if no permanent relief is afforded by curettage, one may then employ sex hormones. For this purpose the most generally effective and least expensive preparation is diethylstilbestrol. Other estrogens are, of course, equally effective if used in adequate dosage, but before employing any such preparation one must remember that estrogens of all types are specifically contraindicated in the presence of a breast tumor.

or family history of cancer of the breast in the presence of cancer of the uterus or in the presence of menorrhagia occurring in the menopausal years. The rationale for the use of estrogens in functional bleeding is to produce and maintain endometrial proliferation thus preventing the breakdown of the endometrium which is responsible for the bleeding. For this purpose stilbestrol should be employed in high dosage. A convenient plan suggested by H. R. Greene which has been found effective is 50 mg. nightly for 4 nights and then 25 mg. nightly for 21 nights. Uterine bleeding will occur in about one week after the last dose. Ordinarily this "menstruation" is not excessive and more or less permanent relief may result. If there is recurrence of the menorrhagia the plan may be repeated three or four times as may be necessary to control the bleeding. This should not be continued indefinitely however and after three or four such trials an other complete evaluation of the case must be made which should include curettage as well as the other inquiries mentioned above. When stilbestrol is used in this dosage a warning should be given that nausea and vomiting may occur. Tolerance is generally developed rather quickly however and the medication should not be discontinued unless there is no improvement after several days trial.

Androgens are also effective in the control of functional bleeding although in the author's experience they are less satisfactory than estrogens. Divided doses of testosterone propionate may be given over a period of one month the total dosage in any one month not to exceed 250 mg. This is reported to give favorable results in something more than 70 per cent of cases. Androgens are suggested particularly for those patients requiring prolonged therapy in whom bleeding recurs repeatedly after it has once been controlled. For this purpose maintenance doses of 5 to 10 mg. of methyl testosterone daily or 10 to 20 mg. of testosterone propionate weekly throughout the cycle are claimed to be effective. When using androgens one must keep in mind the virilizing possibilities with high dosage or in sensitive individuals. All of these effects are considered reversible when the drug is stopped except for voice changes which ordinarily

are permanent once they have been produced.

Finally pitressin tannate in oil has recently been found useful in the management of functional bleeding. A single intramuscular injection of 2 cc. or 10 pressor units is given. The therapy is advocated particularly for the control of the initial episode and is reported to be effective in 1 to 2 days and to last for 2 to 4 days. No formal confirmation of the original report is available at this

antidiuretic hormones are observed.

DAVID N. DANFORTH

REFERENCES

- Benson R. C. The Arrest of Abnormal Uterine Bleeding with Pitressin Tannate in Oil. *Am J Obst & Gynec* 55:286 1948.
Carter A. C. Cohen E. J. and Shorr H. The Use of Androgens in Women in *Vitamins and Hormones*. Edited by Robert S. Harns and Kenneth V. Thimann. New York: Academic Press Inc. 1947. Vol. 5 p. 317.

DYSMENORRHEA

The term dysmenorrhea may have either of two entirely distinct connotations. First it may refer to one of the symptoms of certain organic lesions of the reproductive tract; secondly it may refer to the ill defined condition commonly regarded as an entity of so called idiopathic dysmenorrhea in which no organic abnormality is demonstrable. This chapter is concerned with the latter and presupposes that organic dysmenorrhea is ruled out by a full history and by accurate bimanual examination. The pattern of idiopathic dysmenorrhea is extremely variable. It may start with the first menstruation, more

more or less constant in one individual, may be either days or hours before the onset of the flow, coincident with the onset of the flow or after the flow has started, the pain may last for hours or days, may be mild or

be coincident vomiting diarrhea, or both. Although innumerable articles purport to explain this syndrome, there is as yet no adequate demonstration of a mechanism common to all cases. Hence, therapy remains empirical. The observation that the pain threshold is low in a high percentage of patients with dysmenorrhea is of no interest in management except in the occasional case where psychoneurotic factors or conditions of maladjustment in the home can be shown to operate. Such factors should of course be uncovered and dealt with so far as possible. But irrespective of whether the pain threshold is high or low these patients may not be summarily dismissed as emotionally unstable. They require help, and are entitled to the physician's best effort.

Since therapy is empirical it is necessarily somewhat unsatisfactory. Some cases respond promptly to the simplest of indirect measures, while others are intractable to the most specific efforts.

General Measures In all cases inquiry should be made concerning the patient's habits and also of the reaction of the parents or husband to this periodic illness. This may give valuable information concerning important contributory factors. In addition

hygienic measures including a balanced diet, adequate rest, and healthful exercise out of doors, are important and must not be overlooked.

Exercise It is well known that in many cases of intractable dysmenorrhea, stretching exercises of various types may give dramatic relief. Those recently outlined by Haman have been used by the writer repeatedly and with much satisfaction. They are the following:

Position I Stand at right angles to the wall at such distance as will enable you to rest the left elbow comfortably on a level with shoulder. Tilt the pelvis forward, and, while in this position, touch the wall with the hip, keeping knees straight. Take care not to twist the body or allow the elbow to slide on the wall.

Position II Same as above, using the right elbow.

Position III Face the wall, and rest both

elbows at the level of the shoulder. Tilt the pelvis forward until the pelvis

rests on the wall daily. The extreme exercise of this type, ballet dancing, may appear to be a heroic measure, nevertheless when simple exercises fail, this may be effective, and should be tried.

Medications Any of the analgesic drugs may be employed, some more effectively than others. A combination which has been found useful is a capsule containing

Ephedrine	0.02 gm
Atropine	0.0002 gm
Aspirin	0.3 gm

If this is not effective, because of the severity of the dysmenorrhea, codeine (0.015 or 0.03 gm) may be substituted for the aspirin. It is considered important that the patient have positive relief to fall back on, and codeine should not be denied merely because it is an opiate.

The use of hormones and surgical procedures is not included in the recommendations made here. Some have advocated large doses of estrogens for the purpose of inhibiting ovulation so that the next "menstrual" period will consist only of painless withdrawal bleeding. This is purported to have a salutary psychic effect, although to the writer this seems of dubious value. Progestational and androgenic hormones, except as they may inhibit ovulation are of little use. Surgical procedures may be employed only as a last resort, after all other possibilities have been exhausted. Dilatation of the cervix and insertion of a stem pessary, formerly so fashionable, has fallen into disrepute for the reason that its chief effectiveness is considered to result from the heavy psychologic impact, the appropriateness of which may be questioned. Presacral neurectomy gives a high incidence of relief, but this is a major transperitoneal operation in which even in skilled hands complete removal of the presacral nerve is difficult. It is noteworthy that many prominent gynecologists of wide experience have never found it necessary to employ this procedure for the relief of dysmenorrhea.

Finally, one should remember that it is unusual for idiopathic dysmenorrhea to con-

tinue after a term birth, and that irrespective of pregnancy there is often significant spontaneous improvement after the age of 25 or 27

DAVID N DANFORTH

REFERENCE

Haman J O Exercises in Dysmenorrhea *Am J Obst & Gynec*, 49 755 1945

THE MENOPAUSE

Of all the conditions which the physician is called on to treat, the symptoms associated with the menopause appear to be among the most poorly managed. The important reason for this is the easy availability of preparations which, although they will achieve temporary relief, may have a deleterious effect on the fundamental condition from which the symptoms arise.

At the outset, it should be emphasized that the "menopause" should not be employed to cover bizarre or apparently inexplicable symptoms which may have their onset in the menopausal years. The only symptoms which are characteristically typical of the menopause are the cessation of menstruation and vasomotor disturbances. Other symptoms, even though they may be coincident with those mentioned, demand the same respect which they would receive if they occurred at any other age. Many nervous gastrointestinal and cardiorespiratory disturbances have their onset in both men and women of this age group. To be sure, many such complaints are wholly functional and result from the apprehension and emotional tension which sometimes attend the menopause. But when they exist without at least one of the two fundamental symptoms of the menopause, or when they are not promptly ameliorated by the menopausal therapy outlined below, they must then be considered as unrelated to the menopause *per se* and investigated as such. One often hears of a so-called "therapeutic test with estrogens," in which these substances are given as therapy, for example, of a mild anxiety state or melancholia. In such a case no permanent good may be expected from this therapy, rather, the condition should be recognized as psychiatric, and appropriate measures taken. Also, it should be empha-

sized that excessive bleeding is decidedly not a symptom of the menopause. Too frequently menorrhagia having its onset along with vasomotor symptoms or in the menopausal years, is disregarded. Excessive bleeding at any age demands specific investigation, namely, curettage and microscopic study of the tissue obtained.

Once the diagnosis of "menopausal syndrome" is made, therapy should be directed not toward the achievement of complete relief, but rather toward reducing troublesome symptoms to the point of easy tolerance. With this as a goal it is apparent that therapy must be individualized, and that what is proper for one may be highly improper for another. Measures ordinarily undertaken include the following:

General Measures. Many women of this age group benefit greatly from measures designed to improve their general health. Particular inquiry and investigation should be made concerning such possibilities as low grade anemia or hypothyroidism and if found they should be corrected. Specific advice should be given concerning a balanced diet, rest, diversion from routine household tasks and responsibilities and mild exercise out of doors.

Reassurance. This forms an extremely important part of any regimen, but is perhaps of greatest importance in those who are about to enter the menopause or are experiencing the preliminary symptoms. Well-meaning friends and relatives are often most articulate with respect to the description of symptoms which they have experienced and the "shots" which were necessary for their control. The impact of such reports is heavy, with the result that many women approach the menopause with dread and full expectancy that it will mark the end of their mental vigor and equilibrium. It is of the greatest importance that women be made aware of the facts, first, that by far the great majority of women pass the menopause without incident and second, that a large number of those who encounter difficulty do so for reasons ascribable directly to improper therapy. Also, many women approach the menopause with fears of insanity, or apprehension that sexual desire and satisfaction will be impaired. These women must be reassured that the occasional onset of insanity

has nothing whatever to do with the menopausal pause per se any more than does its similar incidence in men of the same age group, also, it is unusual to find sexual gratification or desire impaired in women who have already established a satisfactory pattern of sexual activity

Sedation In a case in which vasomotor symptoms are less than extreme, and when nervousness and irritability are present mild sedatives are often of great benefit. In fact, most menopausal patients can be controlled with such drugs alone. Phenobarbital in doses of 0.015 to 0.03 gm three times daily, may be given. When sedatives are employed in this manner, the primary objective is to avoid the use of estrogens. However, it is necessary to explain to the patient that she may have some discomfort, and that if it is more than she can easily tolerate other drugs will be prescribed.

Estrogens There are three major principles which govern the use of estrogens in the management of the menopause. These are the following:

(1) Estrogens are orally active, and need not be given parenterally. Controlled studies have demonstrated beyond question that it is only in the exceptional case that oral preparations are not effective and well tolerated by the patient.

(2) The indiscriminate use of estrogens in an effort to eliminate all menopausal symptoms can greatly prolong the menopausal pause.

(3) Estrogens are specifically contraindicated in the presence of a breast tumor or family history of cancer of the breast, in the presence of cancer of the uterus, or in the presence of menorrhagia.

Employing these tenets one proceeds to the estrogen therapy of menopausal symptoms in the following manner. First, a careful examination and history must eliminate the conditions mentioned under (3). Second, the patient must be advised that the objective of this therapy is to reduce the symptoms only to the point where they can be readily tolerated. It is necessary to explain here that although it is quite possible to relieve the symptoms entirely, by so doing the duration of the menopause may be increased. Furthermore, it should be pointed out that the period of time the patient is to

receive estrogens should be limited and should preferably not exceed 6 months.

Many excellent oral estrogens are available. The most commonly employed, as well as the least expensive, is diethylstilbestrol. For the control of ordinary menopausal symptoms, this should be prescribed in doses of 0.5 mg or less at bedtime daily for 2 to 6 weeks, followed by a smaller dose, as 0.2 mg, nightly or every other night for the next 4 to 6 weeks. In occasional cases larger doses will be required, but irrespective of the severity of the symptoms, the smaller doses should be tried first. At the end of this period, the patient should be instructed to decrease the frequency, with the view to eliminating the medication all together within 6 months. At all times the smallest effective dose should be used, and the effort should be made to use this as infrequently as may be possible for adequate control of symptoms.

Occasionally stilbestrol is accompanied by undesirable side effects, such as nausea and vomiting. This is most frequent when doses of more than 0.5 mg are required for control of symptoms. However, tolerance is generally developed rather quickly, so one need not discontinue the medication immediately for this reason. In those whose reaction is marked or where no tolerance develops one may employ other oral estrogens, as premarin, hexestrol, ethinyl estradiol or the like or, exceptionally, hypodermic therapy such as diovocylin 2.5 to 5 mg intramuscularly. Irrespective of what estrogen is used one should be governed by the principles which have been outlined, and should aim specifically at the avoidance of addiction, whether the medication be in the form of tablets, or whether it be "shots."

Androgens Androgens are effective in relieving menopausal symptoms in the same measure as are estrogens and should be employed in like manner and with similar objective. As noted by Gusberg androgens are specifically urged for necessary endocrine therapy of the menopause in the following situations:

(1) Patients who have a family history of cancer of the breast, who have a breast tumor, or who have been treated for cancer of the reproductive tract or breast.

- (2) Patients who have been treated for abnormal uterine bleeding during the climacteric
- (3) Patients who develop troublesome uterine bleeding while under treatment with estrogens
- (4) Patients requiring endocrine treatment for vasomotor symptoms before complete cessation of the menses
- (5) Patients addicted to stilbestrol through long usage

Methyl testosterone may be given by mouth in doses of 20 mg daily for 4 weeks and

then 10 mg daily for 2 weeks. Such doses are ordinarily effective and are generally less than the amounts needed to produce masculinization.

DAVID N. DANFORTH

REFERENCES

- Greene R W and Dorr E M. Relation of Dose and Type of Estrogen to Nausea and Vomiting. *J Clin Endocrinol* 1:821 1941
- Gusberg S B. Androgen Therapy of Menopausal Symptoms in Cancer Patients. *Am J Obst & Gynec* 50:502 1945

TESTICULAR DISEASE

STERILITY IN THE MALE

Treatment of male sterility is begun when it has been established that the wife is apparently normal and that the fault of the childless marriage lies with the husband. Therefore it is essential that the wife have a complete physical examination including a tubal patency test before proceeding with treatment of the husband. It is now recognized that approximately 50 per cent of childless marriages are the result of male sterility.

In order to deal properly with male sterility it becomes necessary to point out the causative factors and their management.

Physiologic Sterility. This condition is found in boys in the prepubertal age group and in old men whose sexual functions have been exhausted. It is hardly necessary to say that no treatment is indicated.

Local Pathologic Conditions. This deals with the absence of testicles either congenital or acquired through injury or surgical castration. There is no treatment for this condition.

- (2) Orchiopexy
- (3) Hormonal therapy with chorionic gonadotropic hormone (anterior pituitary like hormone). One commercial preparation that may be used is korotrin extracted from the urine of

pregnant women and marketed by Winthrop Stearns Company. The suggested dosage is 100 international units given one week later and 200 international units given three times a week for a 6 to 8 week period.

Some cases will show descent in 3 weeks and others will require longer treatment. If there are no results in 8 weeks the hormone therapy will probably not be successful and its administration should then be discontinued.

Another hormone preparation is antuitrin S made by Parke Davis and Company. It is made by extracting the hormone from the urine of pregnant mares. The dosage of antuitrin S as suggested is 500 international units given intramuscularly three times a week. If there is no evidence of response to the treatment after 2 weeks a rest period of 1 month is allowed after which 500 international units are administered again three times a week for 8 to 12 weeks.

In any therapeutic regimen using gonadotropic hormones excessive development of the external genitalia and of the prostate must be prevented. If such growth appears excessive the treatment should be discontinued.

Atrophy and destruction of testicular tissue due to mumps, suppurative orchitis, ischemia of the testes, or roentgen or radium emanations are not amenable to treatment.

Testicular tumors are usually malignant and if enough testicular tissue has been replaced by tumor tissue to cause sterility there is no treatment.

Chronic orchitis is usually due to tuberculosis or syphilis and these diseases are given priority in the therapeutic plan. In any case a chronically diseased testicle probably never will produce adequate healthy spermatozoa.

Prostatovesiculitis may be a factor in sterility. It would seem advisable to clear the seminal fluid of pus which quite possibly would have a deleterious effect on the spermatozoa. The following program is suggested:

- (1) Biweekly prostatic massage and stripping of the seminal vesicles. As the fluid is expressed a drop is examined under the high dry lens of the microscope and the number of pus cells per high power field is counted and recorded. This is done at the time of each massage. In this way the progress can be charted by watching the number of pus cells decrease. Some patients will respond in one or two treatments and others will be more resistant as evidenced by the persistence of high pus cell count.
- (2) Penicillin S R (Parke Davis and Company) is given in single daily intramuscular injections of 800 000 units every other day for a week. Depo penicillin (Upjohn Company) may be given in the same dosage of 800 000 units at each injection.
- (3) Sulfadiazine 0.5 gm given orally with sodium bicarbonate 0.6 gm three times a day for a 7 day period.
- (4) Fluid intake of 8 to 10 glasses of fluid per day is advisable.
- (5) Bowel evacuation if indicated by mild catharsis such as cascara sagrada aromatic fluid extract 1 dr or a 5 grain tablet of cascara given at bed time.
- (6) Complete abstinence from alcoholic beverages and spicy foods.

Obstructions and deformities of the genital tract are treated by surgery where possible. In obstruction of the epididymis and adjacent scrotal portion of the vas deferens epididymovasostomy may be of some help. Obstructions higher than this point cannot usually be corrected by surgery. Hypospadias and urethral strictures are usually amenable to corrective plastic surgery.

General Pathologic Conditions *Endo*

CRINOPATHIES deal with the following conditions:

(1) *Hypothyroidism* The severity of this disease is determined by the history and physical findings including a basal metabolism determination. Thyroid extract will correct this condition.

(2) *Hypogonadism* There is little that can be done for this symptom complex. The benefits obtained from the use of testosterone are questionable because administration of this hormone tends to depress spermatogenesis.

General debilitation and chronic alcoholism are often contributing factors to sterility and they are treated along the lines of prescribing diets high in protein calories and vitamin content.

Vitamin E deficiency is known to be a factor in the production of abortion in animals but its role in sterility is questionable.

Impotence is a factor sometimes met with which causes a pseudosterility in that there may be adequate healthy spermatozoa but the patient is unable to make delivery. The treatment of this condition is discussed elsewhere.

The treatment of sterility begins with the first visit of the patient to the doctor's office. At this time a careful history is taken not only of the duration of sterility, history of mumps, etc., but of a general nature to bring out past diseases and operations which might shed some light on the problem. For example, a patient may be quite fertile but unable to transmit the spermatozoa to the cervical region because of psychologic impotence. Yet this patient will in all probability be most reluctant to discuss his disabilities until the physician wins his complete confidence by tactful questioning in an understanding manner.

At the time of the first visit to the office a physical examination including blood pressure, temperature, pulse rate, urinalysis and rectal digital examination of the prostate is done. Microscopic examination of the prostatic fluid and palpation and inspection of the external genitalia are also recorded. Next the patient is instructed to bring in a speci-

men of semen for examination and spermatozoa count. The specimen is best collected by ejaculating into a wide mouthed bottle at the conclusion of intercourse. The patient should be advised to abstain from coitus for a week before bringing in a semen specimen. Condom specimens are unreliable because the rubber and certain spermicidal powders applied to the sheaths by the manufacturer will give an inaccurate count of nonmotile spermatozoa. The specimen should be brought in to the doctor or the laboratory as soon as possible and not later than 4 hours after intercourse in order to determine accurately the degree of motility of the spermatozoa.

Technic of Counting Spermatozoa

- (1) Diluting fluid is made up with sodium bicarbonate 5.00 gm Formalin 1.00 cc Distilled water 100.00 cc
- (2) After mixing the specimen well draw semen up in a leukocyte counting pipette to the 0.5 mark
- (3) Dilute with the diluting fluid up to the 11 mark
- (4) Allow to stand at least 10 minutes without shaking to permit the sodium bicarbonate to counteract the mucus
- (5) Shake the pipette for 3 minutes
- (6) Plate out the mixture on a counting chamber and count as for a leukocyte count under the high power lens
- (7) Calculate $\times 10^6$ for a leukocyte count and add two zeros to determine the number of spermatozoa per cubic centimeter

Technic of Staining Semen

- (1) Air dry a thick smear on a glass slide
- (2) Stain for 30 to 60 seconds with carbol fuchsin
- (3) Wash gently with water
- (4) Counterstain with methylene blue
- (5) Wash and air dry
- (6) Examine under the oil immersion lens

Semen Requirements for Fertility

- (1) Spermatozoa count of from 60 000 000 to 100 000 000 per cubic centimeter
- (2) About 85 per cent of the spermatozoa must be actively motile
- (3) About 85 per cent of the spermatozoa must be morphologically normal
- (4) The volume of the ejaculate ranges

from 1 to 5 cc. the average being 3 cc

Ambulatory treatment of the patient showing a low sperm count and/or nonmotile or morphologically poor spermatozoa

- (1) Thyroid administration of $\frac{1}{2}$ to 1 grain a day with careful observation for signs of toxicity. Thyroid is given empirically in the absence of evidence of hypothyroidism because an increased metabolic rate has been shown to raise the sperm count and to increase sperm motility
- (2) Hormone therapy with gonadotropic factors is carried out in the same dosage as described under cryptorchism
- (3) General measures such as total abstinence from alcohol adequate diet mild to moderate exercise especially for the sedentary office worker and plenty of rest including at least 8 hours of sleep each night

General Discussion This discussion has been limited to the problem of treating sterility in the male. Several causes have been presented but it must be emphasized that most cases will be due to some unknown or undemonstrable etiology. Therefore the suggested ambulatory treatment will apply in most instances. Reference has been made to certain commercial gonadotropic hormone preparations this is not necessarily an endorsement of these products but a fami-

achieved in the treatment of male sterility will be most gratifying in some cases and discouraging in others but at the present time there seems to be no other way of attacking the problem

JAMES I. FARRELL

IMPOTENCE

Impotence is a condition in which there are varying degrees of inability on the part of the male to have normal sexual intercourse. Impotence is not synonymous with sterility although clinically the two conditions must often be regarded and treated to-

gether A fertile man may be impotent and an impotent man may be fertile, although he is clinically sterile, or rather he has a pseudosterility because of his inability to implant the spermatozoa where they can subsequently fertilize the ovum The degrees of impotence run from premature ejaculation to complete loss of erection

A complete history of the difficulty, particularly of sexual habits, palpation of the prostate with microscopic examination of the prostatic fluid for pus cells examination of the external genitalia, and a urinalysis should classify the disorder as to its underlying etiology, i.e., organic or functional Urethroscopy adds much to the diagnosis and treatment by ruling in or out lesions of the posterior urethra such as inflammation congestion, or such evidence of chronic infection as granulations and polyps about the region of the verumontanum

Impotence may be classified as being of an organic or of a functional nature Treatment of organic causes of impotence depends for its success on the removal or correction of the cause, if possible

Organic Causes LESIONS OF GENITALIA

- (1) Penile inflammations are treated specifically as other infections with chemotherapy and surgical principles
- (2) Curvature of the penis is usually not amenable to treatment because of the nature of the underlying lesion The curvature is due to unequal engorgement during erection of the corpora cavernosa resulting from fibrosis and scar formation, which prevents the blood from distending a portion of the corpus cavernosum Any surgical attempt at removal of the scar tissue is likely to result in more scar formation with unsatisfactory or even worse results
- (3) Urethral strictures are treated by dilations with sounds or by internal urethrotomy, or external urethrotomy, depending on the extent and location of the stricture
- (4) Inflammatory lesions about the verumontanum and granulations and polyps of the posterior urethra respond well to local instillations of silver nitrate, 1 per cent in 3 to 5 cc amounts through a no 14 urethral

soft rubber catheter This may be done once a week for a 4 to 11 week period, at the same time increasing gradually the strength of the silver nitrate up to 2 per cent If this plan of treatment does not help, it is advisable to cauterize the urethral polyps and granulations with the high frequency cautery current transurethral

LESIONS OF THE NERVOUS SYSTEM

- (1) Tabes dorsalis
- (2) Tumors and injuries of the spinal cord
- (3) Cerebral lesions

These lesions are not amenable to the treatment of impotence, also these lesions are serious and of primary importance the impotence is relatively unimportant

ENDOCRINOPATHIES *Frolich's syndrome* may respond quite satisfactorily to treatment with the gonadotropic hormones The same dosage is used in this syndrome as discussed under cryptorchism in the section on Treatment of Sterility in the Male

Absence of testicular tissue may be treated by the administration of testosterone propionate in oil intramuscularly, 10 to 25 mg two or three times a week Methyl testosterone is given orally in doses of 30 to 60 mg daily Because this is a form of replacement therapy, the benefits are derived only as long as the administration of the hormone is continued

Hypothyroidism is best treated by the administration of adequate doses of thyroid substance

PHYSIOLOGIC IMPOTENCE Functional impotence comprises about 95 per cent of the cases that present themselves to the physician However, in order to treat the cause of impotence such cause must be searched for, be it organic or functional There is no indication for treatment of physiologic impotence due to old age There have been attempts, both medical and surgical, at rejuvenation but these for the most part have met with failure Sometimes an older man will seek renewed sexual powers and occasionally he will regain them through one device or another, but the alleged good results are temporary and short lived

Functional impotence may be so complex as to require the services of a psychiatrist However, there are some things that the

physician can do which will offer assistance toward improving or curing the condition. Among these are

- (1) General measures such as improving the general state of health by vitamins, proper diet, adequate exercise, removal of worries and anxieties, and insistence on 8 hours of sleep at night.
- (2) Psychotherapy in the form of impressing on the patient that his difficulty is mental and that he will be cured. An interview with the patient's wife is often essential in order to bring about her understanding of the problem and thus secure her cooperation. Any difficulty in this direction may be overcome by pointing out to her that she, too, benefits from the treatment. The patient with premature or rapid ejaculations is advised

to try to approach the act of intercourse as calmly as possible and to lengthen the time by diverting his thoughts from the business at hand.

- (3) Sedation in the form of elixir or triple bromides, 1 dr twice a day after meals in water, is helpful for the patient troubled with premature ejaculation.
- (4) Hormonal therapy with the gonadotropins probably has little to offer, however, it might be wise to use it empirically as in certain cases of sterility. There are reports of success from hormonal therapy. Whether it is the hormone or the psychologic effect of the needle and syringe on the patient makes little difference. The object is to treat the impotence.

JAMES I. FARRELL

DEFICIENCY DISEASES

VITAMIN DEFICIENCIES

GENERAL CONSIDERATIONS

Vitamins are constituents of enzyme systems and are essential for the metabolism, development, and reproduction of bacteria and animals. Most vitamins are synthesized by the animal organism inadequately, if at all, and the vitamins themselves, or their precursors, must be present in the diet. In their absence, clinical signs of deficiencies and even death may occur.

Although many vitamins exist and have been described, only seven deficiency diseases which have been observed in man and which are of dietary origin are discussed here. Some of the vitamins omitted from the discussion may be essential to man under special experimental conditions. Some, while not synthesized by the body tissues, can be formed in sufficient amounts by intestinal bacteria from precursors and related substances to make up for inadequacies in the diet. Thus, the human dietary requirements may vary widely, depending upon physiologic or pathologic stress and other constituents of the diet, as well as caloric intake.

Prevention of Vitamin Deficiencies

A single foodstuff which in itself supplies an adequate diverse vitamin intake, the diet must be well chosen and should include 1 pt (0.5 liter) of milk, whole or skimmed, or one serving of cheese; one or two eggs, one adequate serving of fish, meat, or poultry; two leafy green vegetables and one yellow vegetable (these may be cooked or raw); one whole grain cereal with additional milk or cream; two slices of enriched bread with 2 teaspoons of butter or vitamin A fortified margarine; freshly prepared citrus

fruit or fruit juice, and another fresh or cooked fruit.

Additional vitamins in concentrated form may be added when the diet is unsatisfactory or is restricted because of obesity, diabetes, or food allergy, when the requirements are increased by infection, surgery, or metabolic disturbances, or to supplement infant feeding where the rapid rate of growth increases the need for vitamins.

Vitamin Preparations The number of mixed vitamin preparations now available commercially and the promotional claims made for each have created considerable confusion. Many preparations include minerals and vitamins for which actual human need has not been proved.

The accepted synthetic vitamins may be used effectively and interchangeably with the natural ones. They are usually much cheaper than the purified vitamins derived from natural sources, but have the disadvantage that they contain none of the trace substances of possible nutritional significance found in the latter.

It is important that the physician have available an authoritative source giving the recognized action, use, and dosage of vitamins, and that he examine the labels of vitamin preparations, comparing them with other products and with the statements and advertising claims offered. The amounts of vitamins in the mixtures used should be related to the dietary requirement. Vitamin mixtures should not supplant preventive and therapeutic dietary measures, but merely supplement them.

Vitamin Requirements In most instances the daily allowances recommended by the National Research Council (1934) are undoubtedly greater than the minimal requirements for health. There is no clinical

evidence that the body stores must be saturated by vitamins for the body to function normally

The possibility that deficiency diseases may develop in chronically ill patients must be anticipated by the physician so that effective prophylaxis or therapy may be instituted. This is also true of other conditions where the normal requirements may be altered as for example during pregnancy. The increased frequency of deficiencies occurring during pregnancy even on a minimally adequate diet suggests that an increased vitamin intake may be necessary at such times.

Sulfonamides are known to affect vitamin synthesis. The effects of the newer antibiotics such as penicillin, streptomycin, aureomycin and chloromycetin on the synthesis of vitamins by intestinal bacteria are still unknown.

While little is known of the vitamin requirements of old people, there is little evidence that the need for vitamins increases

and to poor living conditions and habits. Old people may be confined to their rooms, receive little ultraviolet radiation, have poor appetites and be unable to prepare or eat meals of adequate vitamin content. Improperly fitting dentures or lack of teeth institutes a vicious cycle which may result in gastrointestinal disturbances and still further restriction of the diet. Such manifestations of dietary deficiencies should yield to specific treatment properly administered. Senile

order to treat a patient successfully it is necessary to combine specific vitamin therapy with that of any coexisting disease.

Foodstuffs are best taken by mouth. Parenteral administration is justified for those patients who are unable to take food by mouth or for those having defects in intestinal absorption

and for those with such an acute deficiency that any delay in replacement is inadvisable.

Laboratory procedures which measure vitamin levels in the blood or the amounts excreted in the urine before and after a test dose of vitamins have been employed as diagnostic aids. For the most part they are technically difficult to perform, expensive and subject to misinterpretation. As a result it is the practice of many physicians to give vitamins as a therapeutic test when the patient's dietary history and symptoms suggest an underlying deficiency state. Mild subjective improvement in such a patient is difficult to evaluate. In persons having actual deficiencies the use of a potent purified vitamin compound is usually followed by a satisfactory response in 1 to 3 weeks.

A trial of brewers' yeast or liver extracts or parenteral administration of vitamins or liver may be necessary if oral treatment is ineffective. No benefit can be anticipated unless a need for therapy exists.

There is no irrefutable evidence that healing and regeneration may be hastened or improved by the administration of large amounts of vitamins unless a deficiency exists. There is no rational basis for "overdose" therapy. Although increased excretion of vitamin substances does occur during certain pathologic conditions, an adequate diet is in most instances all that is necessary to compensate for this loss.

Both clinical and laboratory studies have shown that deficiency diseases are seldom due to the inadequate ingestion of only one vitamin. Infantile scurvy and rickets, which may be seen singly and uncomplicated, are exceptions. In general, the necessity for balanced multiple vitamin therapy is accepted and indications for the administration of single vitamin substances are rare.

The interaction of vitamins with each other and the fact that the requirements of one may be affected by the intake of the others have been definitely proved. Excessive dosage of a single vitamin, even if it is nontoxic itself, may precipitate signs of a deficiency of another vitamin. For example, patients with beriberi who are treated with thiamine alone may then develop evidence of a niacin deficiency.

Summary The unrestricted purchase of vitamins over the counter without a doctor's recommendation or prescription should be discouraged. The most dependable source of vitamins are the natural foods of an adequate diet and in most instances families of low income would do better to use the dietary portion of the budget to purchase a good variety of wholesome food rather than purified vitamin preparations. The great amount of publicity given to vitamins has created the erroneous impression that the only way to maintain health is by taking accessory vitamins. It behooves the doctor to consider well whether accessory vitamins are needed and when they are to select carefully the preparation which is best suited to the patient's needs.

DAVID GAYER

VITAMIN A DEFICIENCY

Xerophthalmia and Keratomalacia Vitamin A activity is found in a number of different natural and synthetic chemical compounds. Those found in plants (provitamins A) are converted by the animal liver into substances having vitamin A activity. At least nine naturally occurring provitamins A and two vitamins A are known.

Absorption and Storage of Vitamin A. The absorption of vitamin A and carotenes (provitamins A) is favored by the presence of fat in the intestines. For absorption of carotene bile salts are also necessary. The conversion of carotene to vitamin A in the liver is slow and probably not more than 50 per cent complete. In the presence of liver damage even less conversion occurs. Disturbances of fat metabolism which may be anticipated in such conditions as the sprue syndrome, cystic fibrosis of the pancreas, bile duct obstruction or disturbances of

Chil who
are deficient in pancreatic enzymes can absorb the vitamin A alcohol but require pancreatin for the absorption of the ester (the predominant form).

Interference with absorption by mineral hydrocarbon oils (mineral oil) is exaggerated as a nutrition problem.

Vitamin A is stored in the liver in large

quantities. In persons eating a good diet the vitamin A stores of the liver increase over the years of adult life. Normal individuals with adequate body reserves of vitamin A can go as long as 6 months on a diet deficient in vitamin A before the plasma levels of vitamin A are depleted and often as long as a year before clinical signs of a deficiency develop. In view of the marked ability of the body to store this vitamin indications for parenteral administration are rare.

Requirements of Vitamin A. Recent studies on varying dietary intakes of vitamin A indicate that less than 5000 units daily are required. In adults on daily intakes of 2000 units of vitamin A the blood serum contains 20 to 35 units per 100 cc (Normal 75 + I U), and symptoms of vitamin A deficiency improve. On an intake of 2500 units of vitamin A symptoms of a specific deficiency are relieved and the vitamin A content of the blood reaches normal levels. It would seem therefore that in most instances a daily intake of 2500 units of vitamin A is probably in excess of the amount required to maintain normal nutrition. The daily requirement for women during pregnancy and lactation is probably higher but still below the 6000 to 8000 units recommended by the National Research Council. Infants up to one year of age can probably be maintained on approximately 25 units of vitamin A per kilogram of body weight daily. Present feeding practices make it improbable that they will suffer from an inadequate intake of vitamin A.

In 1946 the A.M.A. Council on Pharmacy and Chemistry refused to accept vitamin A preparations containing more than 25,000 units per dose. The Council was not concerned with the toxic effect of vitamin A but felt that there was no justification for the routine administration of doses in excess of 25,000 units per day.

Therapy BY DIET. The treatment of

precursors. The vitamins A occur in nature only in animal tissue. Vitamin A in the diet is thus derived either preformed from ingested animal tissues or from vegetables as the provitamin. Many carotenoid pigments synthesized by plants are converted by the liver into vitamin A. The foods which con

tribute vitamin A precursors to the diet are yellow and leafy green vegetables such as turnip greens spinach carrots squash and sweet potatoes. Peaches and tomatoes also contain provitamins A. Animal livers are rich sources of preformed vitamin A as are kidneys milk and milk products and eggs. Fortified oleomargarine also contains preformed vitamin A in amounts up to 9000 units per pound.

BY ORAL AND PARENTERAL ADMINISTRATION OF VITAMIN A. There is little reason why any one on a normal varied diet should become deficient in vitamin A. If for any reason the diet is restricted daily supplements of vitamin A up to 5000 international units may be prescribed. This may be given in any of the preparations containing vitamin A alone or in liver oil concentrates containing vitamin A with other fat soluble vitamins. Where a vitamin A deficiency exists vitamin A is preferable to the carotenes for therapy in the treatment of the condition.

A daily supplement of 5000 USP units has been reported to be as effective as 150 000 units given daily. The healing of skin lesions is slow often requiring months. Excessive doses do not result in more rapid healing. In the treatment of various ocular symptoms resulting from a deficiency of vitamin A children who received 25 000 to 30 000 USP units of vitamin A daily did not recover more rapidly than those who received smaller doses. The absorption of vitamin A and carotene from large single doses is limited. Multiple small doses given two to three times a day are therefore more effective therapeutically.

Cod and other fish liver oils are excellent sources of vitamin A. Commercial preparations of vitamin A are chiefly concentrates of fish oil distillates. It is far better to give vitamin A orally than intramuscularly. Parenteral injection of the fat soluble vitamins poses a special problem unless a water soluble preparation of the vitamins is available. Such preparations of vitamin A can be obtained and are suitable for intramuscular injection. When given intramuscularly in oil vitamin A is slowly absorbed. It does not provide an immediate available source for body needs. Utilization of the carotenes after parenteral injection is even less efficient than that of vitamin A.

Other Uses of Vitamin A. Vitamin A therapy has been reported to be beneficial in two rare follicular dermatoses (keratosis follicularis and pityriasis rubra pilaris). In all probability these disorders do not represent

use of vitamin A in the local treatment of burns and wounds. Vitamin A is ineffective

or of no value in the prophylaxis or treatment of acute infections or in enhancing immunologic reactions. The lowered resistance to infection which is associated with severe vitamin A deficiency is probably related to secondary morphologic changes in the protecting epithelial barrier.

Toxicity of Vitamin A. Large doses of vitamin A are well tolerated although intoxication in adults has been reported after as little as 40 000 international units daily. Severe hypervitaminosis A has also been reported in children receiving as much as 240 000 units daily over a period of several years. The condition is characterized by headache drowsiness dizziness dermatitis hepatomegaly splenomegaly hypoplastic anemia leukopenia increased serum lipid and vitamin A levels and clubbing of the fingers. Usually however only normal vitamin A levels are maintained even when excessive amounts of vitamin A are ingested.

Excessive intake of carotene has been reported to result in similar changes. As a rule however a harmless yellow discoloration of the skin which disappears rapidly when carotene is withdrawn is the only manifestation.

Preparations of Vitamin A. Vitamin A is usually prescribed as a fish oil preparation or a solution of carotene the vitamin precursor. Cod liver oil USP contains a minimum of 850 units of vitamin A per gram. The cod liver oil preparations included in the New and Nonofficial Remedies vary in potency from 850 to 2100 units per gram. *The dose must be determined by the strength of the particular preparation used.* The advantage of cod liver oil as a source of vitamin A is its low cost. The disadvantages are the taste and volume which must be taken. It

may, however, be flavored by the addition of not more than 1 per cent of an official flavoring substance

The disadvantage of taste can be overcome by the use of cod liver oil concentrates in capsules. Those included in the New and Nonofficial Remedies contain a minimum of 14 000 units of vitamin A per gram. The vitamin D content is increased proportionately. Natural vitamin A in oil, USP, contains between 50 000 and 65 000 units of vitamin A per gram (1 cc weighs approximately 0.9 gm). Percormorph liver oil contains 60 000 units of vitamin A per gram. It also contains large amounts of vitamin D.

DAVID CATER

VITAMIN B THIAMINE DEFICIENCY

Beriberi. Thiamine is essential in the intermediary metabolism of carbohydrates. It acts as a co-enzyme and by oxidation prevents the accumulation of pyruvic acid in the blood. When deficiencies of thiamine exist severe physiologic cellular disturbances usually most marked in the neurones of the central nervous system occur. Severe and prolonged thiamine deficiency leads to the clinical signs and symptoms of beriberi, in the wet form the permeability of membranes is altered.

Absorption and Storage of Thiamine. Thiamine is readily and almost totally absorbed from the normal gastrointestinal tract and after intramuscular injection excess amounts are excreted after a few hours chiefly in the urine as the free unphosphorylated vitamin. Increased alkalization of the gastrointestinal tract increases the destruction of thiamine. Certain adsorbents such as magnesium trisilicate and kaolin also reduce its absorption.

The vitamin is not stored in the body to a great extent. The total thiamine storage of subjects on a thiamine free diet develop signs of a deficiency in 20 to 40 days.

Requirements of Thiamine. Various estimates of the minimal requirements of thiamine for a moderately active man with a caloric intake of 3000 calories range from 0.2 mg up to 0.5 mg per 1000 calories. It

is felt by most investigators that 0.24 to 0.45 mg of thiamine per 1000 calories will protect against a deficiency of this factor. Others, however, give 0.45 mg as the lower limit of the minimal range for 1000 calories. Deficiencies have been produced on diets containing 0.20 mg per 1000 calories. A diet high in carbohydrate increases the requirement for thiamine, whereas a diet high in fat decreases it.

The studies of Keys and Henschel indicate that healthy young men expending 3740 to 4200 calories per day require no more than 17 mg of thiamine. No additional benefit is derived from the ingestion of 1 mg for each 1000 calories of food.

It has been demonstrated that thiamine can be synthesized by bacteria in the bowel of human subjects and utilized to furnish part of the body's requirement. This is not a major source of supply, however.

It is probably safest to believe that thiamine requirements are increased in lactation, hyperthyroidism and in diseases producing fever or an increase in metabolism. Hence to insure an adequate intake one would have to consider the normal requirement, the amount lost or excreted, alterations in metabolism due to disease, and the previous nutritional state of the individual.

For children under 10 years of age 1 mg daily seems to be adequate to maintain good health.

Therapy of Thiamine Deficiency. By Diet. Heart, liver, kidney, and lean pork are good sources of thiamine. The vitamin is also present in high concentration in whole-grain cereals, enriched flour, tomatoes and fresh green vegetables. Dried brewers' yeast is an excellent source of this vitamin. The thiamine present in fresh yeast is not readily absorbed because the living yeast cell wall resists digestion. In addition to the ingestion of foods with a high thiamine content patients who are deficient in thiamine should eliminate from the diet all vitamin free foods, particularly those high in carbohydrates such as pastries, corn syrup, candy, corn starch and soft drinks.

By Oral and Parenteral Administration of Thiamine. It should be remembered that water soluble vitamins are less adequately stored than the fat soluble group. Hence signs of deficiency may occur in a few weeks.

moderate oral doses of the vitamin

Studies on deficient individuals have shown that 100 to 125 mg of thiamine given orally over a period of 10 to 15 days will usually saturate a patient. When the saturation point is reached the dosage can be decreased to the amount estimated as the daily requirement.

The parenteral administration of thiamine in doses over 3 mg may result in the excretion of a large percentage of the dose, in spite of the subject's need for the vitamin. There is no indication for injecting huge doses of thiamine chloride. Repeated doses of 50 to 100 mg daily may be recovered from the urine almost in entirety if the patients are not deficient. Even in deficient subjects as much as 80 per cent of a 50 mg dose of thiamine may be recovered from the urine within 4 hours. The fact that this loss may be increased by the simultaneous administration of intravenous infusions and the use of mercurial diuretics suggests that thiamine is a threshold substance reabsorbed by the tubules. When the vitamin is given

the solution subcutaneous injection may be quite painful. This drawback is not associated with intravenous administration. The parenteral administration of thiamine in doses over 3 mg is attended by up to a 30 per cent urinary loss.

BERNIERI HEART DISEASE. Congestive failure due to a deficiency of thiamine chloride and occurring as a manifestation of beriberi is uncommon, but not rare. The diagnosis can now be made with reasonable accuracy according to the criteria of Weiss and others. Thiamine chloride is a specific cure for the reversible manifestations of the disease. Treatment has consisted of daily doses of 20 to 50 mg of thiamine given intravenously for a period of 3 weeks. The dose is recognized to be excessive.

Thiamine is ineffective in other forms of heart failure unless a nutritional basis exists.

Other Uses of Thiamine. It is well established that a deficiency of thiamine may produce a syndrome resembling neuritis

themia. Unfortunately, thiamine is of no value in nondeficient individuals with the neurasthenic syndrome. Thiamine chloride alone is ineffective in the treatment of the neurologic manifestations of pernicious anemia. It has no beneficial effect in the treatment of trigeminal neuralgia. It does not relieve the symptoms of radiation sickness. Patients suffering from Huntington's chorea, multiple sclerosis, lateral sclerosis, disseminated encephalomyelitis, parkinsonism, or tabes dorsalis are unimproved by thiamine unless a previous deficiency was present. Patients with Wernicke's disease (acute polioencephalitis) may be benefited by the use of thiamine chloride when the condition is found to be associated with chronic alcoholism and multiple vitamin deficiency. Thiamine is of use in the treatment of diabetes only when it compensates for dietary restriction. Large amounts of thiamine do not reduce the insulin requirement. Altered carbohydrate metabolism does not increase the requirements of thiamine, but the diuresis which occurs in poorly regulated diabetic patients may increase the excretion of the vitamin.

Toxicity of Thiamine. The oral use of thiamine even in amounts several thousand times the therapeutic dose, is said to be without toxic effect. Severe reactions, however, have been reported to follow injection of the vitamin into the subarachnoid space. Allergic reactions consisting of nausea, vomiting, tachycardia, nervousness, and a sense of constriction in the throat may follow the intravenous injection of thiamine and are thought to be the result of a specific sensitivity. Induced sensitivity to the vitamin may result from the repeated injection of thiamine. In sensitive individuals, the intramuscular or intravenous injection of thiamine may be followed by nausea, sneezing, vaso-dilatation, urticaria, cyanosis, and even death. In such instances death is apparently due to anaphylactic shock.

In allergic individuals, particularly those who have received injections of thiamine previously, intradermal tests should always be done before thiamine is given intravenously. The oral administration of thiamine

5 mg 10 mg and 50 mg Thiamine hydrochloride tablets for oral use are usually available in doses of 1 3 5 and 10 mg

DAVID CAYER

VITAMIN B NIACIN DEFICIENCY

Pellagra Niacin is present in all living cells. It occurs in tissues as the amide and is an essential part of co enzymes 1 and 2. It functions in glycolysis and the intracellular respiratory function of all cells. It serves to transfer hydrogen to other respiratory catalysts forming carbon dioxide and water and releasing energy.

Pellagra is a well recognized clinical syndrome which is due to malnutrition and which can be corrected or prevented by the ingestion of a sufficient quantity of good protein or in most instances by sufficient niacin.

Absorption and Storage of Niacin Niacin and its amide are readily absorbed unchanged from the normal gastrointestinal tract and from parenteral sites of injection. The principal excretory product N-methyl niacinamide is formed in the liver and can be found in the urine. There is experimental evidence of niacin synthesis in the bowel which persists even when sulfonamides are given. The effects of oral penicillin and streptomycin on the synthesis of this vitamin are not yet known.

Niacinamide is present in small amounts in all living cells. There are no special sites of storage in the body although higher quantities are found in the liver and adrenal glands than elsewhere.

Requirements of Niacin The minimal daily requirement of niacin is difficult to estimate. It is altered by numerous factors which include the activity of the individual, the level of protein consumption, the quality of protein in the diet, the presence of pellagragenic substances, the caloric intake, the ingestion of corn, and the extent of bacterial synthesis in the bowel.

Niacin deficiencies which occur in persons eating large quantities of corn are due not to the lack of a niacin precursor but to an amino acid imbalance with a relative lack of tryptophane which results in an increased demand for niacin. The presence of the niacin precursor and a protein which furnishes

a physiologically balanced amino acid mixture on digestion accounts for the pellagra preventive properties of such foodstuffs as milk and eggs which are almost devoid of niacin. The increased demand for niacin in persons ingesting large amounts of corn is thus due to the large quantity of tryptophane, deficient protein and the unbalanced amino acid mixture which increases the demand for niacin.

The National Research Council recommends 18 mg of niacin daily for a moderately active man weighing 70 kg. This recommendation allows a margin of safety and a smaller intake does not imply that the diet is deficient. Pellagra is rare where wheat or rice, even polished rice, is the chief cereal of the diet although as little as 5 mg of niacin per day may be ingested as such. Persons eating milk, eggs, leafy green vegetables and little corn are protected by 12 to 15 mg per day. Where corn is the staple food 25 mg of niacin per day may be required.

It is probably best for the present to adhere to the recommended daily allowance although the figure is high and the requirements are probably less than 10 mg per day in most instances. The influence of disease on the niacin requirement is not definitely known although it is probably increased by illness.

Therapy By Diet The best form of treatment for pellagra is to provide the patient with a diet which contains adequate amounts of both niacin and pellagra preventing foods. These foods consist of any animal liver, lean meat, turnip greens, spinach, green or black eyed peas, tomatoes, yeast and bran. Peanuts and peanut butter are good sources of niacin. Eggs and milk, though low in niacin content, are important because of the quality of the protein supplied. The diet should include a quart of milk daily, 4 oz of fresh lean beef liver, canned salmon, chicken or lean pork and flour or bread to which niacin has been added. The food should be given at regular and frequent intervals and special care taken to see that it is eaten. When diarrhea is present, symptomatic control may be helpful in increasing the absorption of niacin.

By Oral and Parenteral Administration of Niacin Adequate amounts of niacin properly administered are highly specific for the

clinical manifestations of pellagra, and usually result in prompt and often dramatic improvement. The ulceration and soreness of the mouth and tongue, the mental symptoms, and the dermatitis, anorexia, and diarrhea usually show evidence of regression in 2 to 4 days. During this period symptomatic treatment, including special oral hygiene, therapy of infected skin lesions, control of excessive peristalsis, and correction of dehydration, should be begun.

The multiple factors which probably produce the deficiency, as well as the known difficulty of saturating pellagrins with niacin, seem to justify the use of large doses over a long period of time (3 to 4 months). Cures can be produced with 50 to 100 mg per day by mouth, although cases requiring 300 to 500 mg per day have been reported. Spies and his associates have recommended as much as 500 mg per day, given in divided doses. They feel that the higher doses have greater efficacy. The possibility of concomitant fatty infiltration of the liver in pellagra (and in alcoholic cirrhosis) and the potential damage which can result from excessive doses of niacin should be considered.

The administration of niacin by mouth or parenterally is often followed by flushing and a burning, tingling sensation of the skin. The reaction is harmless, and larger doses do not increase the severity of symptoms. They can be reduced by administering the drug with or after meals. Since niacinamide is equally effective and eliminates the unpleasant side effects, it is the preferred form of the drug for administration by any route. When liver damage is present, use of the amide is probably indicated.

Since multiple deficiencies are likely to be present, a supplementary intake of other B complex vitamins, in addition to a good diet, is a necessary adjunct in the treatment of active pellagra. In niacin deficiencies the time required to produce saturation with the vitamin is probably longer than that required in uncomplicated thiamine or riboflavin deficiencies, and longer periods of therapy (months) are therefore —

gm per day are suggested. This may be given in divided doses in milk or tomato juice. Fresh bakers' yeast is of little value.

INFANTILE PELLAGRA In African infants and children with a syndrome of malnutrition which resembles pellagra, Gillman and Gillman state that massive doses of B complex vitamins administered orally or paren-

place in the liver and produce metabolic disturbances which can no longer be corrected by vitamins administered alone or in combination with lipotropic factors. They feel that large amounts of niacin are contra-indicated in the treatment of severe infantile pellagra. They found the use of ventriculin (5 gm twice daily by mouth), in addition to a good diet (without supplementary vitamins), to be more effective than liver by injection or diet plus vitamins. If ventriculin was not available, liver extract by injection was the treatment of choice.

Other Uses of Niacin The vasodilating effect of niacin has been the basis for its use in the treatment of myalgia, arthritis, Menière's syndrome, coronary artery disease, fibrositis, and headache. The drug must be

nary vasoconstriction and should be used with caution. The efficacy of niacin therapy in these conditions is still doubtful.

A complete list of disorders which have been reported to respond favorably to niacin is not worth while, since in most instances further study has failed to confirm early claims. The efficacy of niacin in clearing up the mental symptoms of pellagrins has led to the use of this vitamin in other forms of mental disease. A beneficial effect in the encephalopathy of alcoholics occurs only if a niacin deficiency exists. The chief indication for niacin therapy is in the prevention and therapy of deficiency states.

Toxicity of Niacin The toxicity of niacin is low. The most important single effect of the drug is the transitory vasodilatation, which is accompanied by a sensation of heat, tingling, and itching, and occasionally by urticaria. Nausea, diarrhea, dizziness, and vertigo occur infrequently. The effects are

day) is of value. Dried brewers' yeast is a rich natural source of niacin. As much as 100

THERAPEUTICS IN INTERNAL MEDICINE

transitory and do not occur when the same dose is given after meals or when the amide is administered. In normal individuals derivations of niacin are relatively innocuous.

Preparations of Niacin. Sterile solution of 100 mg of niacin in water for parenteral use. Niacinamide for parenteral use in doses of 100 mg in 1 cc and 100 mg in 2 cc. Niacin (U.S.P.) tablets—25 mg and 50 mg. Niacinamide (U.S.P.) tablets—25 mg and 50 mg.

DAVID CATER

VITAMIN B RIBOFLAVIN DEFICIENCY

Riboflavin is an essential constituent of oxidative enzymes and functions in cellular respiration.

Deficiencies of riboflavin are considered by some observers to be widespread and particularly prevalent in the South. However, the wide distribution of riboflavin in plant and animal tissues would suggest that clinical deficiencies of riboflavin should be uncommon. In all probability cheilosis and vascular invasion of the cornea which are often regarded as pathognomonic of ariboflavinosis are more often expressions of other deficiencies or are nonspecific.

Absorption and Storage of Riboflavin
Riboflavin when ingested or when given in small parenteral doses is absorbed easily and apparently is retained according to the needs of the patient. It is synthesized in significant amount by bacteria in the bowel and may not be a dietary essential under all conditions. The synthesis is less susceptible to interruption by sulfonamide therapy than is that of thiamine.

The reserves of riboflavin are not great but they are less rapidly depleted than those of thiamine. Riboflavin stores in the normal individual who is placed on a deficient diet are depleted slowly during a period of as long as one month. Thus a patient whose intake is limited for less than 2 or 3 weeks requires no more riboflavin than enough to cover his daily requirement. Since the storage of riboflavin is dependent on an adequate protein intake, protein must be administered to promote the storage of the riboflavin given. Excess riboflavin is excreted in the urine unchanged.

Requirements of Riboflavin
The agreement has still not been reached as to the riboflavin requirements in man. It states that an intake of 0.35 mg of riboflavin per 1000 calories does not meet "requirements," however, studied normal young men on diets were limited to 0.31 mg of riboflavin per 1000 calories (the daily diet contained an average of about 0.31 mg of riboflavin) and found no ill effects. In a group of subjects maintained on a daily diet of 2000 calories containing 0.7 mg of riboflavin, none of the characteristic cutaneous or lingual signs of ariboflavinosis developed. The National Research Council, however, proposes 0.9 mg per 1000 calories as the minimum daily requirement for a moderately active adult male weighing 70 kg.

Prophylaxis and Treatment of Riboflavin Deficiency By Diet
Prophylaxis and treatment consist in making available to the patient an adequate supply of the vitamin. Dietary sources of riboflavin are liver, lean meat, eggs, milk, cheese, leafy green vegetables, dried yeast (1 oz daily added to cereal, fruit juice or milk), green peas, enriched flour and butter. The riboflavin in live yeast is poorly absorbed.

By Oral or Parenteral Administration
Well developed riboflavin deficiencies should be treated until the symptoms clear up with oral doses of 1 to 2 mg of riboflavin given three times daily, in addition to an adequate diet. It is important to remember that many of the signs once thought to be pathognomonic of riboflavin deficiency are not specific and that deficiencies of niacin and other members of the B complex may also be present. In such cases the symptoms will not disappear until full and adequate therapy with multiple vitamins is instituted. The treatment of corneal ulcers and infiltrations with riboflavin is rapidly effective in a matter of days when the lesions are due to the specific deficiency.

Occasionally the parenteral administration of riboflavin is effective when oral administration is not. Improvement will usually follow intramuscular injections of 1 mg of riboflavin given daily for 3 to 4 days. Deficient subjects will retain up to 75 per cent of a 1 to 2 mg dosage given parenterally. Normal or saturated

to 100 per cent of such a dose in the urine unchanged the riboflavin gives the urine a deep yellow color. In patients with severe riboflavin deficiencies a total dosage of 40 to 50 mg. divided into small oral doses given several times a day will saturate the patient in approximately 10 days unless other complicating disorders have radically altered the metabolism.

Toxicity of Riboflavin No toxic effects from enormous doses of riboflavin have been noted in human beings; the excess is excreted in the urine within several hours.

Preparations of Riboflavin Riboflavin tablets (USP) are available in 1 and 5 mg. sizes. A sterile solution of riboflavin in water (1 mg. in 2 cc., 5 mg. in 1 cc.) is available for injection; this solution may contain other suitable agents to increase solubility such as urea or macinamide. Riboflavin readily precipitates out of solution as dark crystals; the precipitation is accelerated by light.

DAVID CAYER

VITAMIN C DEFICIENCY

Scurvy Ascorbic acid (vitamin C) is generally considered to participate in oxidation-reduction reactions in the body and in cellular respiration, although its precise function is unknown. Chemically it is a strong reducing agent and hence is quickly and easily oxidized. When it is absent from the body, normal intracellular "sticky" substance is not formed and the clinical manifestations of scurvy appear. Vitamin C is essential for life since it is not synthesized by man; a continuous source of supply is necessary to maintain health. Prolonged depletion produces the clinical syndrome of scurvy and ultimately results in death.

Scurvy is now primarily a problem of infancy, although it may occur in aged individuals subsisting on diets markedly deficient in vitamin C.

Absorption and Storage of Ascorbic Acid Ascorbic acid, either synthetic or natural, is rapidly absorbed from the intestines after ingestion. It is stored in many organs, particularly the adrenal cortex and liver. In the presence of a vitamin C deficiency a

reduced form by the kidney makes it possible to determine the point at which saturation of the body stores is reached. Ascorbic acid is also excreted in sweat and milk.

The body stores of vitamin C are not large. In otherwise normal individuals who are given a diet containing no ascorbic acid, symptoms of scurvy appear within 5 to 10 months. Thus patients who are unable to take foods containing vitamin C or who have been on a previously deficient diet should be given ascorbic acid. Adequate protection is probably afforded for at least 4 months by normal body stores. In all proba-
months

imates of the minimal daily requirement of vitamin C for an otherwise healthy adult range from 25 mg. to 100 mg. per day. The standard

and ensure saturation.

Scurvy has been produced experimentally by limiting the intake of ascorbic acid to 10 mg. per day. Similar studies have indicated that a daily diet containing 25 mg. of vitamin C or possibly less will protect against scurvy and ensure wound healing. On dosages of 25 to 75 mg. of ascorbic acid per day tissue reserves are increased and saturation of body stores usually takes place. An intake in excess of 75 mg. per day usually results in saturation and rapid excretion of the excess ascorbic acid in the urine. Where the requirements are increased as for example in lactating women as much as 150 mg. per day may be necessary. The difficulty in producing saturation of the body stores in patients with febrile diseases, leukemia or hyperthyroidism probably indicates a greater destruction of this vitamin and an increased need for it in these patients.

There is no indication that it is necessary or beneficial to maintain complete saturation if a constant daily intake is assured.

Prevention and Treatment of Scurvy By Diet The prevention and treatment of scurvy consist in providing the individual with sufficient amounts of vitamin C. The

daily requirement could be supplied in entirety by 8 oz of freshly prepared citrus fruit juice or 1 pt of canned tomato juice. An 8 oz. glass of orange juice plus a similar amount of fresh tomato juice will supply 150 mg of vitamin C. Fresh vegetables provide a stable source. Cabbage, turnips, baked potatoes, and tomatoes are excellent sources, as are cantaloupes and orange, tomato, lemon, or grapefruit juice. The advantage of citrus fruits is that they are regularly eaten raw.

Ascorbic acid is destroyed by oxidation, but not by heat. It should be remembered that fruit juices which are prepared and allowed to stand, particularly if uncovered, in iron or copper receptacles, depreciate rapidly in vitamin content. This depreciation occurs whether the juices are refrigerated or not, though cooling slows the rate of oxidation. In addition, the ascorbic acid in vegetables is reduced by exposure to light and by prolonged storage whether refrigerated or not. The addition of soda to vegetables during cooking reduces the vitamin C content materially, since this vitamin is destroyed more rapidly in an alkaline medium. Achlorhydria and antacids may also affect the destruction and stability of ascorbic acid in the bowel, and may reduce the amount absorbed.

By Oral or Parenteral Administration of Ascorbic Acid. Patients with frank scurvy can be saturated with vitamin C by doses of 100 mg given by hypodermic daily for 7 to 10 days. A larger dose of 500 mg of ascorbic acid may be given orally three times a day. For most patients deficient in ascorbic acid a total of 1500 mg will produce saturation of the body stores. Where a prolonged deficiency of ascorbic acid has preceded treatment, 1500 mg daily for 2 or 3 days may be required. The tourniquet test for capillary fragility may be used as a clinical test of response to therapy, the signs of increased capillary fragility disappear within 24 hours after the body requirements for vitamin C have been met.

Ascorbic acid is water soluble and is suitable for parenteral injection. Occasionally clinical scurvy may not respond to vitamin C given orally, but will disappear following intramuscular or intravenous administration of the vitamin. It acts as a threshold sub-

stance and is excreted in the urine. Since the intravenous injection of a large dose of vitamin C elevates the plasma level more than an oral dose of similar size, a greater amount is excreted.

Crystalline ascorbic acid may be dispensed in tablet form in dosages of 25 mg per day, or dissolved in propylene glycol to supplement the formulas of young infants unable to take fruit juices. Where it cannot be taken orally, intramuscular injection is more economical than intravenous administration, since less is lost through the kidneys following the injection.

Exceptions to the above statements regarding the dosage and quantity necessary for saturation may be found in patients having leukemia or certain metabolic disorders and in those receiving intravenous fluids or diuretics which produce excessive excretion. Otherwise, once the body has been saturated, 75 mg of ascorbic acid daily is more than enough.

Other Uses of Vitamin C. The Sippy diet and other bland diets used for gastrointestinal disturbances are frequently low in vitamin C. In addition, these patients may complain of digestive disturbances following the ingestion of fruit juices. In such individuals the administration of the purified vitamin concentrate may be necessary to make up for the dietary inadequacy.

Anemia. There have been numerous reports of hematologic studies made on patients with naturally occurring or experimentally induced scurvy. Anemia, which may be normocytic or macrocytic, may occur. In general, however, scurvy and anemia do not necessarily coexist. Constant blood loss or lack of iron and dietary essentials other than ascorbic acid usually accounts for the anemia. In some patients, however, after all other factors have been corrected, hematologic and clinical improvement will occur only when crystalline vitamin C is administered. In these patients a reticulocyte response will be noted in 5 to 8 days. It must be emphasized that these patients all show clinical signs of an ascorbic acid deficiency.

There is no apparent relationship between iron and ascorbic acid in the synthesis of hemoglobin. The concomitant administration of iron does not prevent the utilization of

ascorbic acid, and an excess of vitamin C is of no value in the therapy of anemias not associated with scurvy

Wound Healing In severe scurvy, wound healing is delayed or absent. Such a degree of depletion in the average surgical patient, however, is most unlikely. In patients in whom no clinical evidence of a vitamin C deficiency can be demonstrated and in whom demonstrable levels of vitamin C can be found in the blood plasma there is no decrease in wound healing.

alone

It has been reported that the simultaneous administration of 250 mg of ascorbic acid with mercurhydrin will decrease the toxicity of the latter without affecting its diuretic action. It has also been reported that vitamin C counteracts the toxic action of arsenicals in man without impairing their therapeutic efficacy. This effect is said to be most favorable when both the arsenical and vitamin are injected in the same solution. There remains, however, some difference of opinion as to the value of ascorbic acid as a detoxifying agent.

Gingivitis The diagnosis of a vitamin C deficiency on the basis of gingivitis alone is unwarranted as is the attempt to cure all types of gingivitis with vitamin C.

In general it may be said that ascorbic acid has little usefulness except in the prevention and cure of scurvy.

Toxicity of Vitamin C There is no evi-

tablets (U.S.P.) containing 25, 50 and 100 mg are available for oral administration. Ampules containing 100 mg dissolved in 10 cc of sterile distilled water may be had for intramuscular and intravenous use.

DAVID CAYER

VITAMIN D DEFICIENCY

The name "vitamin D" is given to a number of sterols which are capable of preventing and healing rickets and producing normal mineralization of bone. Vitamin D

promotes the intestinal absorption of calcium and phosphorus, and maintains the blood concentrations of these substances necessary for the normal calcification of bone. The vitamins D are formed in or out of the body, before or after ingestion, from the inactive sterol by ultraviolet irradiation or other physical processes.

Although many vitamins D are known at the present time, vitamins D₂ and D₃ are the most important in man and have almost equal therapeutic powers. Vitamin D₂ (calciferol) is the active substance in viosterol, drisdol and many other potent antirachitic preparations. It is formed by the irradiation of ergosterol and contains 40,000 international units of vitamin D per milligram. Vitamin D₃ (activated 7 dehydrocholesterol) is the natural vitamin produced in the human skin by exposure to ultraviolet rays.

Absorption and Storage of Vitamin D Vitamin D is absorbed from the gastro-intestinal tract from parenteral sites of injection, and through the skin. Normally, a considerable amount of the vitamin is obtained from exposure of the body to sunlight. Apparently the vitamin D formed in the skin is absorbed into the blood stream. Ingested vitamin D is absorbed largely from the small intestine. Absorption is increased by the presence of moderate amounts of fat and the presence of bile. Vitamin D is not well absorbed by many persons with obstructive jaundice unless bile salts are also administered.

There are no special sites of storage for vitamin D in human beings. The vitamin is probably stored to some slight extent by all body tissues. There is evidence that the vitamin is stored in the body for 3 to 6 months following the administration of large amounts. Some vitamin D is metabolized, some is excreted through the intestine (25 per cent). It is also excreted in milk.

Requirements of Vitamin D **FOR CHILDREN** The requirements for vitamin D depend on the rate of growth, the amount of exposure to sunshine and the foods eaten. The daily requirement of children from birth up to 15 years of age probably varies between 400 and 800 international units. The prophylactic requirement for premature infants is thought to be as much as twice that of full term infants until the second year of

life, because of the more rapid rate of growth. A daily intake of 500 international units will usually protect full term infants and young children. Higher allowances up to 800 international units, provide a wider margin of safety. Where ample exposure to sunshine is obtained, smaller amounts of vitamin D are required in the diet.

FOR ADULTS The adult's requirement for vitamin D is unknown. It is probably 800 to 400 international units per day. A supplement of 700 international units of vitamin D, in addition to an adequate calcium intake, is recommended for mothers during pregnancy and lactation. The requirements for vitamin D appear to be higher at this time than at any other period.

Prophylaxis The ingestion of vitamin D is required only when the human organism is not exposed to sunlight or other sources of ultraviolet rays and is thus unable to synthesize vitamin D. The provitamins D which are activated by irradiation, are found in many plants and animals. Vitamin D, however, is scarce in nature. The foods which contain the greatest amounts are eggs but ter milk, and liver. The fish liver oils are the best source of this vitamin. Since they may vary considerably in antirachitic potency the dose must be adjusted according to the content of vitamin D.

In regions where ultraviolet irradiation is scarce during the winter months, many children are unable to produce their own vitamin D. They must be given supplementary amounts of the vitamin to prevent rickets. Cod liver oil is the best known source of vitamin D although its concentration is below that of many other fish liver oils. In doses of equivalent units, percomorph oil, cod liver oil, viosterol, and crystalline vitamin D are equally effective in the prevention and treatment of rickets.

NORMAL FULL-TERM INFANTS Vitamin D, 300 to 400 units, per day supplied by evaporated or irradiated milk is sufficient to prevent rickets in most full term, normal infants. By the end of the second week, 200 units of vitamin D per day should be given, and the dose increased to 400 units by the end of the first month. Parks recommends even greater amounts, 800 to 1200 units, for the remainder of the first year, and 800 units per day throughout the second year. In most

instances this higher amount will be well tolerated, and can be given in any of the accepted preparations of vitamin D. It is best to give this by dropping it on the tongue or directly into the mouth during feeding. If it is given in milk, a preparation miscible with water should be used, since the oil may remain on the sides of the bottle.

PREMATURE INFANTS Premature infants are highly susceptible to rickets. The requirements for such infants are higher than those for a full term baby. As a rule, 800 to 1200 units of vitamin D per day will prevent the clinical manifestations of rickets in premature infants, although in some instances the daily intake may have to be raised to 20,000 to 30,000 units for a time. The individual requirements govern the dosage. Calcium salts should be given in addition to vitamin D at the onset of treatment.

SINGLE MASSIVE DOSE THERAPY Vitamin D can be demonstrated in the circulating blood 2 to 3 months after a single oral dose of 200,000 units. Following the administration of daily doses, levels of vitamin D in the blood serum remain normal for 3 to 6 months. For this reason, some have advocated the use of single massive doses of vitamin D, for which they claim the following advantages: (1) They eliminate the usual daily dietary supplement, and are therefore timesaving; only two oral doses per year, one during the winter and one in the spring months, are required. (2) Loss by regurgitation of the feeding is less likely to occur.

Some investigators feel that single large doses of vitamin D should be administered parenterally to obviate the possibility of poor absorption or improper administration. They also advise parenteral administration when infants are premature, when intestinal absorption is poor, or when intestinal disturbances are present.

The size of the dose depends on the age and weight of the infant and the time interval between doses. Infants receiving a single dose of 300,000 or 400,000 units of vitamin D will not develop rickets for a period of 8 weeks following injection. Two hundred thousand units, however, cannot be depended upon as a single prophylactic dose.

Two general plans of treatment are recommended.

(1) At the age of 1 month 50 000 units of vitamin D are given 50 000 units at the age of 2 months and 600 000 units after 3 months. The first two doses are administered with the baby's formula. The third is given with precooked cereal in divided doses 24 hours apart. A repeat dose of 600 000 units may be given from 3 to 6 months later depending on the needs of the infant the season and the clinical findings. When an infant is obtaining adequate sunshine the repeat dose may be deferred until the onset of winter. A dose of 600 000 units may then be given two or three times during the next year.

(2) A dosage of 1000 units of vitamin D is given each day until the age of 3 months. Then 600 000 units is given and this dose is repeated 4 months later. In October and the following January 600 000 units can then be given.

Vitamin D is a powerful and dangerous drug and the administration of massive doses requires careful supervision by the physician. The margin of safety is great however unless toxic levels are maintained over a period of time. In children with nephritis polycystic kidneys or pyelonephritis the use of large doses of vitamin D predisposes to metastatic calcification in the kidneys and other organs and is therefore contraindicated. Repeated examinations of the urine blood pressure and blood calcium should be made during treatment.

Rickets. Vitamin D concentrates should be used in the treatment of rickets since premature infants may require as much as 10 000 to 20 000 units per day. In the majority of cases however 1200 units per day will suffice. In rare instances the use of oral or intramuscular doses as high as 600 000 units may be necessary. Effective treatment usually produces roentgenographic evidence of healing within a period of 2 weeks. Such treatment must include an ample intake of calcium and phosphorus. This is supplied when an adequate amount of milk is given (1 to 1½ liters). If necessary supplementary calcium may be given as calcium gluconate lactate or dibasic phosphate (1 gm three times a day).

Cases of "refractory" rickets are occasionally seen beyond infancy. The usual dose of vitamin D is ineffective in curing these chil-

dren and enormous amounts are necessary. Treatment should be begun with daily doses of 500 000 to 1 000 000 units of vitamin D and continued until evidence of healing is noted. The dose should then be reduced to lower levels.

The hypocalcemia associated with instances of "renal" rickets is secondary to disturbed renal function. It is accompanied by elevation of the blood phosphates and nonprotein nitrogen and should not be treated with vitamin D.

Osteomalacia. This condition is often termed "adult rickets." It is uncommon in the United States. Treatment is similar to that of rickets. Therapeutic doses of vitamin D (7500 to 15 000 units daily) are recommended along with a generous intake of calcium (1.5 gm. daily).

Senile Osteoporosis. The relation of this disorder to osteomalacia and the efficacy of vitamin D in its treatment are still undecided. Hormonal influences and a diet deficient in proteins may be contributing

caution in regulating the dosage and duration of treatment.

Hypocalcemic Tetany. Tetany is often associated with rickets and may be due to inadequate dietary intake or poor intestinal absorption of calcium and a deficiency of vitamin D. The immediate symptoms are best controlled with 5 to 20 cc of a 5 to 10 per cent solution of calcium gluconate given slowly by vein or intramuscularly. Vitamin D and a diet high in calcium are useful in the subsequent treatment of hypocalcemic tetany. A high intake of vitamin D (100 000 to 500 000 units per day) will increase calcium absorption. Calcium lactate or calcium gluconate may be dissolved in water or milk and given in doses of 1 to 2 gm three times a day. Acid producing salts such as ammonium chloride (1 to 2 gm three times a day) or dilute hydrochloric acid are also of value since calcium is ionized and absorbed better in an acid medium. Where laryngospasm is marked morphine (1 mg per 5 kg of body weight for infants) may be administered by hypodermic or avertin (50 to 100 mg per kilogram of body weight) may be

given in a 1.25 per cent solution as a retention enema

The treatment of hypoparathyroid tetany with dihydrotachysterol (A.T. 10) a substance related to vitamin D is discussed elsewhere

Other Conditions Large doses of vitamin D have been employed in the treatment of arthritis. Editorial comment from the *Journal of the American Medical Association* sums up the present opinion. Critical examination of the reports on the value of vitamin D in the treatment of chronic arthritis reveals little to warrant the belief that the beneficial effects claimed are specific

The use of vitamin D in tetany due to causes other than hypocalcemia in the treatment of psoriasis and acne and to induce calcification in trichinosis is of dubious value

Toxicity of Vitamin D Individual tolerance to vitamin D varies but there is little danger of toxic reactions if reliable preparations are given in amounts less than ten times the preventive antirachitic dose. In most instances the margin between therapeutic and toxic levels is large. The vitamin D preparations known to have produced toxic effects include fortified cod liver oil irradiated ergosterol and electrically activated vaporized ergosterol. Instances of vitamin D poisoning in infants receiving 20,000 to 40,000 international units daily over a period of several months have been reported. A daily dose of 20,000 international units per kilogram of body weight is usually considered as the minimum toxic dose for human beings. Toxic reactions are usually due to irradiated ergosterol given in high concentration. Toxic effects from cod liver oil are unlikely

The most frequent symptoms of vitamin D poisoning are anorexia, nausea, vomiting, occasional diarrhea, polyuria, muscular weakness, lassitude, headache and depression. If the vitamin D is continued it may produce skeletal decalcification, calcification of the kidney tubules and other organs and death. When signs of vitamin D intoxication are detected the dose must be reduced or the drug withdrawn. As might be anticipated the danger is greatest in children where the dose of vitamin D is larger in proportion to body weight and symptoms may not be detected early.

Preparations of Vitamin D **FORTIFIED FOODS** The vitamin D content of some natural foods has been increased by artificial means. The foods are fortified with vitamin D either by feeding the vitamin D and its precursors to the animal which provides the food stuff or by adding concentrates directly to the food particularly bread, cereal and milk. Foods fortified with vitamin D are labeled as such.

NATURAL AND SYNTHETIC PREPARATIONS A partial list of commonly used natural and synthetic preparations of vitamin D appears below. It is important to remember that natural oils contain vitamin A in high concentrations whereas preparations of artificially activated vitamin D do not unless they are enriched.

The vitamin D content of the better cod liver oils is two to three times the USP requirement. One teaspoonful (4 gm.) will supply between 340 and 1000 units depending on the potency. All doses must be administered in terms of the potency of the preparation used. The more potent preparations may be dispensed in proportionately smaller amounts.

The potency and dose of cod liver oil concentrates vary with the preparation.

Cod liver oil with viosterol contains 850 units of vitamin A and 360 units of vitamin D per gram. The daily recommended dose for normal full term infants and adults is 2 to 4 cc. for premature infants and the treatment of rickets 8 cc.

Percomorph oil is a rich source of vitamin D. It is put out in varying concentrations. The preparations are labeled according to the number of units per gram.

Viosterol contains 10,000 units of vitamin D per gram. One cubic centimeter equals approximately 0.9 gm. The recommended daily dosage for full term infants and adults is 5 drops for premature infants or the

for normal full term infants and adults is 5 drops (2 to 3 drops if given in fortified milk) for premature infants or the treatment of rickets 15 to 20 drops

DAVID CAYER

VITAMIN K DEFICIENCY

The term "vitamin K" is applied to that group of compounds which can be utilized

fest by a tendency to hemorrhage and a lowered prothrombin level of the blood

Absorption and Storage of Vitamin K The naturally occurring vitamin K is fat soluble and the presence of bile salts is required for its absorption. Where bile is absent from the intestine as in obstructive jaundice or biliary fistulas hypoprothrombinemia is common.

Since assays of tissues reveal that little vitamin K can be stored the time required for depletion may be only a matter of days. The synthetic precursors of vitamin K are not stored but some are absorbed from the bowel in the absence of bile salts.

Requirements of Vitamin K The exact requirements of vitamin K for human beings are not known. They are probably quite low however and 1 to 2 mg. of pure vitamin K, if properly absorbed and utilized will correct a deficiency. Prothrombin is formed rapidly by the liver and a deficiency can be corrected in a matter of hours.

Sources of Vitamin K Two naturally occurring vitamins K are known. Vitamin K₁ is present in green leaves and is widely distributed in plants. Spinach, cabbage, cauliflower and kale are good sources. Fruits are poor sources. Vitamin K₂ is synthesized by a variety of bacteria from almost any food in the human intestine. *Escherichia coli* produces the vitamin even in a simple culture medium. Yeast however does not contain it.

Prophylaxis and Treatment of Conditions Characterized by Hypoprothrombin

• 1 AL L F

Additional vitamin K is of no value

In the treatment of hypoprothrombinemia frequent laboratory determinations of the prothrombin content of the blood must be

used as a guide since the levels may drop acutely. Satisfactory simple micro and macromethods requiring only minutes to run are available. The prothrombin time in seconds varies with the local standard and is usually reported as the percentage of normal. Bleeding usually is manifested at 20 per cent. In the absence of liver damage a reduced prothrombin time is an indication of a depletion of vitamin K stores.

Hemorrhagic Disease of the Newborn If the mother is obtaining an adequate diet sufficient vitamin K is absorbed to provide the fetus with normal prothrombin levels. In the winter months when the mother's diet may be low in vitamin K the fetus may not store enough of the vitamin to be protected during the first week of postnatal life. The administration of sulfonamides or salicylates to the mother may also depress the prothrombin level of the baby. The use of mineral oil by the mother probably interferes little with the absorption of vitamin K.

A deficiency of vitamin K in the infant is characterized by bleeding during the trauma of delivery and during the first week of life and is accompanied by a low concentration of prothrombin in the blood. Within 12 hours after birth the prothrombin often begins to drop progressively if the stores of vitamin K are not replenished. When hemorrhage occurs the decrease in circulating prothrombin is even more marked. When the infant's dietary source is derived solely from milk and bacterial synthesis in the bowel has not yet become established dangerously low levels may occur if the vascular system is uninjured however bleeding may not be manifested.

Opinion concerning the prophylactic use of vitamin K varies. Some clinicians recommend the parenteral administration of vitamin K to all mothers during labor and to the babies after birth in an effort to provide maximal protection to the baby. Others feel that the low prothrombin levels found in newborn infants are physiologic and tend to be misleading. They feel that the low incidence of hemorrhagic disease of the newborn (less than 0.5 per cent of all infants) makes it foolish to waste vitamin K on the remaining 99.5 per cent particularly since the water soluble preparations offer a prompt means of treatment for those showing hemor-

rhagic tendencies Since the possibility exists, however, that a low prothrombin level in a newborn infant may result in uncontrollable bleeding if a vascular injury does occur during delivery, the prophylactic administration of vitamin K to the mother seems justified. Investigators are not agreed on the optimal time of administration before labor and the correct dose. Since there is no evidence of a cumulative effect it would seem useless to give the drug for more than a week prior to delivery. If the mother has received no vitamin K, a dose of 1 mg. of menadione (a fat soluble synthetic precursor) given orally each day during the last week of gestation or 2 to 5 mg. of a water soluble preparation given by mouth 2 to 5 hours before delivery is adequate. Intramuscular injection of 2 to 5 mg. of an aqueous preparation is equally satisfactory. The parenteral administration of vitamin K to mothers in labor brings the prothrombin content of the blood in both mother and infant to normal levels in 1½ to 4 hours. The usual fall in prothrombin between the second and fifth day of life is not present when adequate vitamin K is given to the mother during labor or to the infant after birth.

When bleeding occurs in a newborn infant, 2 to 5 mg. of a water soluble preparation should be injected intramuscularly or intravenously without waiting for a laboratory diagnosis of hypoprothrombinemia. The need for additional therapy can be decided later by determining the prothrombin time. It is important that newborn infants requiring surgery be given vitamin K preoperatively.

Bleeding Due to Inadequate Absorption of Vitamin K. In the absence of bile salts, absorption of natural and fat soluble vitamin K is faulty, and a fall in prothrombin may result. Hence low levels should be anticipated where obstructive jaundice or biliary fistulas exist. When the reserve supply is depleted, the fall in prothrombin may be rapid. A single prothrombin determination indicates only the circulating prothrombin level. It gives no information as to the amounts stored or the body's ability to maintain a normal blood level. Thus a jaundiced patient whose prothrombin time was normal before operation may begin bleeding shortly after operation. Factors which may be re-

sponsible for the depleting of vitamin K stores include the loss of blood, the reduction of hepatic function caused by anesthesia, and the subsequent anorexia, and limitation of the diet, the preoperative use of drugs which inhibit the synthesis of bacterial flora may also play a part.

Hypoprothrombinemia due to the lack of bile may be prevented or treated by the oral administration of menadione and bile salts or a water soluble preparation of vitamin K orally. With the latter simultaneous administration of bile salts is not necessary. Two to 5 mg. of menadione given orally with bile salts will maintain a normal prothrombin time for 2 to 3 days. Where more rapid therapeutic results are desired intramuscular injections of one of the water soluble preparations is advisable. These have 50 to 70 per cent of the vitamin K activity of a similar amount of menadione. If intramuscular injections are used 4 mg. of the water soluble substances given every 2 or 3 days is sufficient. If given intravenously, 2 mg. daily is an adequate dose. If massive bleeding or shock becomes apparent, whole blood or plasma should be given to compensate for the time lag in the restoration of prothrombin levels.

Gastrointestinal Disorders. The hypoprothrombinemia which accompanies intestinal disturbances is due to faulty absorption of vitamin K. It is particularly apt to occur in instances of steatorrhea. In such patients the parenteral use of vitamin K is indicated. Two milligrams of menadione or its equivalent per day are usually adequate. The need for larger doses or prolonged treatment can be ascertained by determination of the prothrombin level and will depend on the response of the steatorrhea to other treatment.

Since prothrombin is synthesized in the liver, primary parenchymatous disease of the liver diminishes the synthesis and storage of the vitamin. Effective therapy in such instances must be designed to treat the hepatitis. Where such efforts are successful, the production of prothrombin is rapidly restored. In the less severe forms of hepatitis the prothrombin rarely drops to critical levels. The use of vitamin K in these patients is of little help. Vitamin K is probably not indicated in the treatment of cirrhosis except where blood loss has already occurred.

In such cases it may be helpful in preventing a drop in the blood prothrombin level secondary to the hemorrhage.

Decrease in Prothrombin Formation*
Dicumarol retards the synthesis of prothrombin producing a fall in prothrombin levels within 2 to 3 days. In patients receiving dicumarol, synthetic vitamin K was first noted to produce little effect, but it is now

water soluble synthetic precursor) will usually cause the prothrombin time to fall to safe limits if dicumarol is discontinued simultaneously. These doses of vitamin K were given without ill effects. A definite lowering of prothrombin time usually occurs within 2 hours and reaches a maximum in 18 hours. The need for subsequent treatment can be evaluated by determining the prothrombin time.

The hypoprothrombinemia induced by salicylates can be prevented by vitamin K. In general salicylates in therapeutic doses (up to 10 gm daily) produce only moderate prothrombinopenia. However, it is wise to administer vitamin K prophylactically to patients with rheumatic fever who are receiving salicylates or sulfonamides and in whom an operative procedure such as a tonsillectomy is being considered. The dosage of vitamin K which will counteract the prothrombinopenia produced by a given quantity of salicylates cannot be accurately determined, although it is probably in the neighborhood of 1 mg of menadione for 1 gm of acetylsalicylic acid.

* Recent studies by Miller, Harvey and Finch question the actual value of synthetic vitamin K preparations in returning the coagulation defect produced by dicumarol to normal. These observers feel that vitamin K (2 methyl-3 phytyl, 4 naphthoquinone) and vitamin K oxide menadione (2 methyl-1, 4 naphthoquinone) are far more potent than the usual vitamin K preparations. These substances may be obtained from Merck and Company and are most efficient when given intravenously in a dose of 0.5 to 1 gm. No toxic effects were noted but it must be emphasized that although the danger of serious hemorrhage may be averted with the use of these drugs the danger of thrombo-embolic complications continues to be present.—Ed for

Miller, R. Harvey, W. P., and Finch, C. A. Antagonism of Dicumarol by Vitamin K Preparations. *New England J. Med.*, 242:211, 1950.

Congenital Hypoprothrombinemia
Instances of idiopathic hypoprothrombinemia in otherwise normal individuals have been reported. When it occurs in females 2 to 5 mg of menadione prior to menstruation may prevent excessive hemorrhage and a further drop in prothrombin levels. A daily intake of 1 mg is probably advisable as a prophylactic procedure. Therapeutic doses would be necessary only where the prothrombin is below the 20 per cent level and considerable blood is lost.

Other Uses of Vitamin K
Vitamin K is of value in the treatment of menorrhagia only when the prothrombin is reduced.

Hemorrhage occurring with blood dyscrasias or accompanying peptic ulcer may produce prolongation of the prothrombin time if vitamin K reserves are low.

The assumption that prothrombin provides cellular nutrition and influences capillary permeability has led to the use of vitamin K in the management of urticaria. It is of doubtful value in this condition.

Toxicity of Vitamin K
Vitamin K in therapeutic doses seems to be nontoxic. Eight milligrams of menadione have been given daily by mouth to human patients over a period of 30 months without signs of toxicity. Two hundred milligrams of synkavite (a brand of water soluble synthetic vitamin K) given intravenously to normal individuals produced no ill effects. The toxic dose of synthetic naphthoquinones so greatly exceeds the therapeutic dose that there is little, if any, toxic reaction in routine treatment.

In human beings a toxic dose of vitamin K produces vomiting and a fall in blood pressure. Daily doses of 10 mg or less by mouth are entirely nontoxic, and 20 mg daily of the water soluble preparations can be given intravenously for weeks without untoward effects. The drug, however, was found to be irritating to the skin and mucous membrane when applied locally as an ointment. In general the margin of safety between the effective therapeutic dose and the toxic dose of vitamin K is so great that it may be considered to be practically nontoxic.

Preparations of Vitamin K
Naturally occurring substances with vitamin K activity have been supplanted by active synthetic products.

Menadione (2 methyl 1 4 naphthoquinone) is available in 1 2 and 5 mg tablets for oral use and in 1 cc ampules containing 2 mg dissolved in oil for intramuscular use

A series of related water soluble compounds has also been synthesized. When given intravenously the water soluble substances with vitamin K activity quickly provide a temporary supply of vitamin K to the liver. These compounds include such preparations as

Hykinone (2 methyl 1 4 naphthohydroquinone-3 sodium sulfate) available in ampules of 10 and 40 mg for intravenous use and in 48 mg tablets

Synkamun (4 amino 2 methyl 1 naphthol hydrochloride) available in 4 mg capsules for oral use and in ampules containing 1 mg per cubic centimeter for parenteral use

Synkavite (2 methyl 1 4 naphthohydroquinone diphosphoric acid ester tetrasodium salt) available in 5 mg tablets for oral use and in 10 cc ampules for intravenous use

DAVID CAYER

REFERENCES

General Cayer D. Recognition and Treatment of Early Vitamin Deficiency States. *JAMA* 132:558 1946

Ingelfinger F J. Medical Progress: Parenteral Use of Vitamin Preparations. *New England J Med* 233:379 1945

Jolliffe N, McLester J S and Sherman H C. Prevalence of Malnutrition. *JAMA* 118:944 1942

Ruffin J M, Cayer D and Perlzweig W A. Relationship Between the Clinical Picture of Mild or Early Vitamin Deficiency and Laboratory Determination of Vitamin Levels. *Gastroenterology* 34:340 1944

Vitamin A. Booker L E and Callison E C. Minimum Vitamin A Requirements of Normal Adults: Utilization of Carotene as Affected by Certain Dietary Factors and Variations in Light Exposure. *J Nutrition* 18:459 1939

Cayer D, Crescenzo V M and Cody S. Plasma Vitamin A Levels in Pregnancy: Relationship to Total Plasma Lipids. *Am J Obst & Gynec* 54:259 1947

Cayer D, Ruffin J M and Perlzweig W A. Vitamin Levels in Sprue. *Am J Med Sc* 210:200 1945

Clifford J. The Effects of

El Carotene and Vit 165

1937 Sandels M R et al. Conjunctivitis in School Child

dren as Expression of Vitamin A Deficiency. *Am J Dis Child* 67:101 1941

Wohl M G and Feldman J B. Occurrence of Avitaminosis A in Diseases of Liver. *Am J Digest Dis* 8:464 1941

Thiamine. Hibbs R E. Beriberi in Japanese Prison Camp. *Ann Int Med* 25:270 1946

Keys A et al. Performance of Normal Young Men on Controlled Thiamin Intakes. *J Nutrition* 26:399 1943

Weiss S and Wilkins R W. Disturbance of Cardiovascular System in Nutritional Deficiency. *JAMA* 109:786 1937

Wilder R M. Thiamine Deficiency. *M Clin North America* 27:409 1943

Williams R D et al. Observations on Induced Thiamin (Vitamin B₁) Deficiency in Man. *Arch Int Med* 68:785 1940

Niacin. Elvehjem C A. Relation of Nicotinic Acid to Pellagra. *Physiol Rev* 20:249 1940

Gallman T et al. Substitution of Whole Stomach Extract for Vitamins in Treatment of Malnourished Infantile Pellagra. *Nature London* 154:910 1944

Handler P. Present Status of Nicotinic Acid. *Internat Ztschr Vitaminforsch* 19:593 1949

Spies T D, Cooper C and Blankenhorn M A. Use of Nicotinic Acid in Treatment of Pellagra. *JAMA* 110:699 1938

Taylor F R and Cayer D. Pellagra in Oxford. *Medicine New York*. Oxford University Press Inc. 1947. Vol 4, p 307

Riboflavin. Cayer D, Ruffin J M and Perlzweig W A. The Clinical Significance of Glossitis and Cheilosis in Deficiencies of B Complex. *South M J* 33:111 1945

Ferrebee J W. Urinary Excretion of Riboflavin. Fluorometric Methods for Its Estimation. *J Clin Investigation* 19:551 1940

Hogan A G. Riboflavin Physiology and Pathology. *JAMA* 110:1188 1939

Sehrell W H and Butler R E. Riboflavin Deficiency in Man: Preliminary Note. *Pub Health Rep* 53:998 1938

Williams R D. Observations on Induced Riboflavin Deficiency and Riboflavin Requirement of Man. *J Nutrition* 23:381 1943

Vitamin C. Crescenzo V M and Cayer D. Plasma Vitamin C Levels in Patients with Peptic Ulcer: Response to Oral Load Test of Ascorbic Acid. *Gastroenterology* 8:754 1947

Holland A H Jr, Canniff J C and Bruger M. Evaluation of Vitamin C Status of Human Sub-

King C G. Physiology of Vitamin C. *JAMA* 111:1095 1938

Pujos M and Lozner E L. Vitamin C Economy in Human Subject. *Bull Johns Hopkins Hosp* 75:303 1944

1937
Human
111:703

1938

- Park E A Use of Vitamin B₁₂ Preparations in Prevention and Treatment of Disease *JAMA* 111 1179 1938
- Sheldon W et al Dosage of Vitamin D (Report of Subcommittee of British Paediatric Association) *Post Grad Med J* 18:905 1912 also *Am J Dis Child* 65:158 1913 also *Arch Dis Child* 1943 18:58 1943
- Vollmer H Treatment of Rickets and Tetany by Parenteral Administration of One Massive Dose of Vitamin D *J Pediatr* 16:419 1940
- Wolf I J Further Observations on Use of Single Massive Doses of Vitamin D in the Prevention of Rickets *J Pediatr* 24:167 1944
- Vitamin K Allen E V Clinical Use of Anticoagulants Report of Treatment with Dicumarol in 1686 Postoperative Cases *JAMA* 134:373 1947
- Cromer H E and Barker N W Effect of Large Doses of Menadione Bisulfite (Synthetic Vitamin K) on Excessive Hypoprothrombinemia Induced by Dicumarol *Proc Staff Meet Mayo Clin* 19 217 1944
- Hellman L M Moore W T and Shettles L B Factors Influencing Plasma Prothrombin in Newborn Infants Study of Vitamin K Activity of Various Naphthohydroquinone Derivatives *Bull Johns Hopkins Hosp* 66:379 1940
- Quick A J Action of Various Drugs on the Prothrombin of the Blood *J Lab & Clin Med* 31:168 1916
- Quick A J and Grossman A M Nature of Hemorrhagic Disease of Newborn Delayed Retention of Prothrombin Level *Am J Med Sc* 199:1 1910
- Shapiro S Studies on Prothrombin Effect of Synthetic Vitamin K on Prothrombinopenia Induced by Salicylate in Man *JAMA* 125:548 1944 correct on 125:973 1944
- Cromer H E and Barker N W Effect of Large Doses of Menadione Bisulfite (Synthetic Vitamin

THE SPRUE SYNDROME

Successful therapy of the sprue syndrome is dependent on recognition of the origin of the varied manifestations. Most clinicians group together under the diagnosis of sprue at least three separate entities: (1) acute sprue (both "tropical and nontropical"), (2) partially or completely refractory sprue (chronic sprue often called "nontropical sprue") and (3) steatorrhea of idiopathic origin with or without accompanying anemia. Patients with any of these complexes exhibit evidences of gastrointestinal malabsorption particularly of fats and fat soluble substances. Macrocytic anemia with megaloblastic arrest is present in true sprue and may accompany idiopathic steatorrhea.

The gastrointestinal malabsorption may result in the development of conditioned deficiencies of calories (weight loss), protein (hypoproteinemia), vitamin K (hypoprothrombinemia), calcium and vitamin D (hypocalcemic tetany and osteoporosis), vitamin A (nyctalopia), vitamin C (scurvy) and perhaps other factors. In cases of idiopathic steatorrhea anemia may be conditioned by malabsorption of hemopoietic vitamins. Accordingly therapy must be directed at treatment of the anemia at correction of or compensation for the underlying absorptive defect immediate remedy of any clinically manifest or latent conditioned deficiency (such as hypoprothrombinemia or hypocalcemia) and the provision of an abundant

diet to replenish the body content of depleted nutrients.

The microcytic anemia encountered in the sprue syndrome responds satisfactorily to folic acid (pteroylglutamic acid) in daily doses of 5 to 15 mg orally or parenterally. Concentrated liver extract (15 units per

to 300 units is administered. The recently isolated vitamin B₁₂ is reported to be hemopoietically active in sprue but the optimal therapeutic dose of this new vitamin cannot be stated at this time. It may approximate (in micrograms) the dosage schedule recommended for liver extract since 1 microgram of vitamin B₁₂ seems to approximate 1 unit of liver extract.

Maintenance therapy is frequently required for patients with sprue unless pronounced sustained dietary changes can be induced. Satisfactory specific maintenance will be provided most patients by 5 mg daily of folic acid orally or by periodic intramuscular administration of liver extract in amounts sufficient to supply an average of 1 unit daily. Evaluation of maintenance by vitamin B₁₂ cannot be made at the time of writing.

Unless acute sprue has become partially or completely refractory the gastrointestinal

manifestations are usually well controlled by folic acid or liver extract. In idiopathic steatorrhea or refractory sprue these manifestations are but partially or poorly controlled by specific agents and there is a marked tendency to relapse. Many of these patients are benefited by the oral administration of an agent which enhances the emulsification of fat and thereby promotes the absorption of lipids and fat soluble substances. Such an agent is polyoxyethylene sorbitan mono oleate ('Tween 80') which is useful in improving the absorption of fats in a variety of absorptive difficulties, including cases of the sprue syndrome. The dosage of this agent which has been used is 15 gm with each of three meals daily.

The prompt control of the accompanying conditioned deficiencies may be of utmost importance, particularly is this true of bleeding due to hypoprothrombinemia and of tetany. The measures necessary for their treatment are essentially those employed for the same deficiencies wherever encountered. Prothrombin levels will be readily restored by small parenteral doses of a vitamin K preparation such as 2 mg of menadione or by oral administration of, preferably, a water dispersible derivative of vitamin K such as menadione tablets in 2 to 5 mg dosage. The tetany and osteoporosis are more difficult to control and require more prolonged therapy. Acute attacks of tetany are relieved by intravenous injections of 10 cc of calcium gluconate, rebreathing may be of value for milder attacks. Serum calcium levels can usually be increased slowly by the oral administration of calcium chloride, 1 or 2 teaspoonfuls of a 33 per cent solution in water with three meals daily and a vitamin D preparation some 5000 to 20,000 units daily. Theoretically, water dispersible preparations of vitamin D should be the more effective. In some instances the control of tetany may present a stubborn problem requiring trials of other agents, as dihydro tachysterol, which serve to promote calcium absorption and retention.

Conditioned scurvy responds readily to daily quantities of 200 to 300 mg of ascorbic acid in divided doses for a few days. It is rare to encounter vitamin A deficiency of the severity requiring specific measures. If avitaminosis A is clearly manifest, daily admin-

istration of 10,000 to 25,000 units of vitamin A should suffice to control it, particularly if given with an emulsifying agent.

The rare patient with sprue will exhibit a concomitant iron deficiency anemia due to excessive blood loss, sometimes caused by intestinal parasites. Where this occurs, the administration of the usual oral dose of 0.3 gm of ferrous sulfate three times daily for a few weeks will relieve this deficiency. If intestinal parasites are present, the appropriate therapy should be instituted.

Adjustment of the pattern of dietary intake to provide an abundant allowance is basic in the successful therapy of the sprue syndrome. No magic pattern of diet exists for treating this disease. Inasmuch as the treated patient is building new body tissue and has an inefficient absorption of foodstuffs generally, and has low body reserves of nutrients, it is obvious that an abundant intake of calories, protein, and protective foods is in order. Initially a moderately low fat diet may be desirable in order to prevent aggravation of the existing steatorrhea. The acutely ill patient may not tolerate overfeeding. Frequent smaller servings should be given instead of larger quantities in the usual three meals daily. With the response to specific therapy, however, it is seldom necessary or desirable to continue a low fat regime. The diet should contain 100 to 130 gm of protein, a goodly portion of which should be derived from animal sources (lean meat, liver, milk, eggs, cheese). Daily menus should provide a variety of vegetables (both root and leaf), fruits, meats, and dairy products. Frequent inclusion of organ meats (liver, heart, kidney) in the menus is desirable because of their high nutrient content. Efforts should be made to persuade the patient to continue such a regimen after recovery from the acute illness.

During the stages of acute illness and early remission it is desirable to permit the patient to exercise cautiously in order to reduce the possibility of thrombophlebitis or orthostatic pneumonia.

The immediate treatment, therefore, of the acute case of sprue consists of specific therapy with a hemopoietic factor and correction of recognizable evidences of other deficiencies and dietary adjustment. After recovery of body weight and vigor (several

months), it may be advisable to withdraw specific therapy and test the ability of the patient to maintain himself on an abundant diet alone. If relapse occurs it may not become evident for a year or more, hence observation of the patient should be sustained over a period of considerable time after withdrawal of specific therapy. Should evidence of relapse be detected, reinstitution of specific therapy should be made.

WILLIAM J. DARBY

REFERENCES

Castle, W. B., et al. Etiology and Treatment of Sprue, Observations on Patients in Puerto Rico

- and Subsequent Experiments on Animals *Arch Int Med*, 56:627, 1935
- Darby, W. J., Jones, E., and Johnson, H. C. Effect of Synthetic *Lactobacillus Casei* Factor in Treatment of Sprue *JAMA*, 130:780, 1946
- Darby, W. J., et al. Influence of Pteroylglutamic Acid (Member of Vitamin M Group) on Gastrointestinal Defects in Sprue. Study of Interrelationships of Dietary Essentials *J Nutrition*, 34:645, 1947
- Hanes, F. ■ Diagnostic Criteria and Resistance to Therapy in Sprue Syndrome *Am J M Sc*, 204:436, 1942
- Ingelfinger, F. J. Diagnosis of Sprue in Nontropical Areas *New England J Med*, 228:180, 1943
- Miller, D. K., and Barker, W. H. Clinical Course and Treatment of Sprue *Arch Int Med*, 60:385, 1937

ANOREXIA NERVOSA

Introduction This discussion of the treatment of anorexia nervosa is based on the premise that the state of starvation which characterizes this condition is secondary to a psychic disturbance and that the endocrine disturbances which occur are in turn secondary to the starvation. It is apparent that this concept necessarily discredits the diagnosis of Simmonds' cachexia which is frequently made when this clinical picture is presented. It is equally apparent that the widespread acceptance of the concept of Simmonds' cachexia has retarded general recognition of the true basis for this symptom complex. The manifestations of starvation which are observed in anorexia nervosa are not associated with the complete and permanent anterior pituitary insufficiency which is implicit in the diagnosis of Simmonds' disease. It has been shown repeatedly that the supposedly irreversible clinical picture which frequently has led to this erroneous and hopeless diagnosis is actually completely reversible. These symptoms and findings are more aptly referred to as the depressant effects of starvation and many of them are probably attributable to the depressant effects of starvation on the function of the glands of internal secretion.

The results of investigative work as well as clinical observation have led us to suspect that the origin of some of the manifestations of starvation may rightfully be placed in certain of the glands of internal secretion. For example, the lowered basal metabolic

rate, which serves as a mechanism of protection for the starving individual, can perhaps be attributed to failure in production of the thyrotropic hormone. A failure in production of the adrenocorticotrophic hormone most likely is responsible for the common findings of low values for both 17 ketosteroids and cortin like substances (11-oxysteroids) in the urine, impairment of diuresis following the ingestion of large quantities of water (a similar result being observed in Addison's disease) and the frequent finding of relative lymphocytosis which likewise characterizes Addison's disease. The low blood pressure, slow pulse rate, and marked weakness, the last of which is commonly seen in older individuals, and not uncommonly seen in young individuals who exhibit marked emaciation, likewise can be ascribed in part at least to a lack of adrenocorticotrophic hormone. The unexplained pallor which occurs without anemia and which characterizes the victim of anorexia nervosa suggests a dysfunction of the anterior lobe of the pituitary body, for similar pallor is one of the prominent recognizable findings of anterior pituitary insufficiency. While the amenorrhea of anorexia nervosa has been attributed either to psychic disturbances or to the effects of starvation, its direct cause can be traced to a lack of gonadotropic hormone, for the resumption of menstruation may be foretold by the reappearance of prolactin and estrin in biologic assays of the urine. The over all picture from the labora-

tory point of view ■ that of severe but reversible anterior pituitary insufficiency It is the recognition of this reversibility which has given to this clinical entity ■ hopeful rather than ■ hopeless prognosis

Treatment The attitude of the physician and his ability to obtain and hold the confidence of the patient ■ the secret of successful treatment The actual treatment of the manition itself is a simple problem of dietetics

THE APPROACH *Consideration Given Emotional and Psychic Disturbances* The physician must remember at all times that he is dealing with ■ individual who is psychically and emotionally disturbed He also should keep in mind that many of these patients are well above the average in intelligence In many cases the attitude of the patient's family toward her * illness previous unsuccessful attempts at treatment and previous erroneous diagnoses have produced a skepticism toward all therapeutic suggestions Because of these mental peculiarities no fanciful explanations should be attempted and the discussion should be sincere straightforward and impersonal It is of equal importance that the patient not be antagonized while receiving a minimal amount of sympathy In this manner the physician seeks willing co operation and once the patient's confidence is obtained the physician may be surprised by the degree of enthusiastic co operation Such an attitude toward the patient has the tendency to dis-

should be that it is important that the treatment of each individual patient and the consultations with her be limited to the supervision of one physician

It is advisable to reserve psychiatric studies or a discussion of the psychic and emotional disturbances until the patient has recovered from the debilitating effects of the illness Premature efforts to probe the peculiarities of the personality of the patient often induce an antagonistic attitude which renders systematic therapy difficult Adequate time for

obtaining information concerning the psychic disturbance is afforded during treatment and suggestions for correction of causative situations may be given when recovery is well under way Subsequent pointed psychiatric examinations are unnecessary except for academic interest

Preliminary Discussion The preliminary discussion with the patient and her relatives is of great importance as without this complete co operation can hardly be expected The dietetic basis for her manition an outline of the treatment to be carried out and the reason the treatment is to be carried out in the manner to be described should be explained to the patient in detail before treatment is begun Sufficient time should be given to this discussion in order that the patient may understand the problem and what is expected of her It is important to discuss the patient's symptoms with her and to explain to her that these symptoms have been the result of the starvation which she has undergone It should be pointed out that the distress and the feeling of fullness and distention after meals have resulted from the progressively lessened amount of bulk in her diet over a period of time and that in this manner she had trained herself to become intolerant to more than a small amount of food at any one time

It should be explained that the treatment is aimed at the reverse procedure that by progressively increasing the amount of bulk in her diet at mealtime she will gradually become accustomed to this increase and that a point will be reached at which the postprandial distress will gradually lessen and disappear The patient should be reassured that in spite of her aversion to food and her postprandial symptoms the treatment will cause her no great discomfort and that her aversion to food will decrease ■ a part of her recovery It should be pointed out however that she should expect some increase in the postprandial distress during the first few increases in the diet but that it is necessary that she tolerate this before her symptoms become less She should be assured that by putting up with this preliminary distress she will reach a point at which the caloric value of the diet will allow her to overcome her manition

If vomiting has been present it should be

* Anorexia nervosa occurs in the male but with such comparative infrequency that for reasons of facility in presentation no reference is made to males

explained much in the same manner and on the basis of its being a conditioned reflex. The active stimulus for this reflex is a sense of fullness which with the passage of time has occurred at a lower and lower threshold and has appeared when less and less bulk has been present in the stomach. No increase in the bulk of the diet which should be initially small should be attempted until vomiting has been overcome.

Roentgenoscopic studies of the stomach are prerequisites to treatment if for no other reason than to reassure the patient that no obstruction exists at the outlet. She also should be reassured that the stomach was found to be of normal volume as these patients not infrequently will make the statement that their stomachs have shrunk.

The patient should be told that usually the time required to increase her diet to the required amount will be approximately 6 weeks, one week being necessary for each increase of 300 calories. It should be emphasized however that the primary interest in this 6 weeks of treatment is not in the amount of weight gained in that time but in the fact that at the end of that period she will

so that
on the
and the
ive re-
turned to her standard weight and will have been relieved of the symptoms caused by her inanition. In the event of co operation a promise of complete recovery from all symptoms and changes secondary to starvation can be given with impunity with the one exception of amenorrhea. The latter is dependent on the degree and duration of the starvation and its duration should not be predicted.

DIETARY TREATMENT The series of events which accompany gradual decreases or increases in the bulk of the diet is entirely subjective and must be listed under the heading of psychosomatic phenomena. A situation analogous to this variability of the "comfort capacity" of the stomach is seen in the physiologic similarity manifested in the urinary bladder during the development of as well

as during the recovery from the condition known as "habit frequency."

Sudden increases in the bulk of the diet such as starting patients who have been taking 1300 calories or less on a diet with a value of 3000 calories are followed by upper abdominal distress, lack of confidence and co operation and consequently failure. However small increases in the bulk of the diet may be made at regular intervals without causing the patient sufficient discomfort to

theless increasing a high protein diet by 300 calories at a time will gradually increase the bulk of the diet. A rough estimate of the patient's daily caloric intake prior to admission is made and to this amount are added 300 calories. The patient is given a high protein high vitamin diet based on that number of calories (1300 to 1600 calories or less) and is asked to eat everything served her. For the first few days she may complain of distress and a sensation of fullness; however after several days these symptoms begin to lessen. After 5 or 6 days the caloric content of the diet may be increased by another 300 calories. For the next 2 or 3 days discomfort after meals may be experienced again; however the symptoms again gradually become less. This procedure is repeated until the daily intake reaches 3200 calories. These patients experience far less distress from eating this amount than they had experienced after the meals of the initial diet which was based on 1300 calories or less.

The food values of the diets as used in caloric increases are given in Table I.

TABLE I
FOOD VALUES IN DIETS

Carbohydrates	Protein	Fat	Calories
gm	gm	gm	
115	71	60	1300
150	73	79	1600
187	75	93	1900
219	80	114	2200
245	83	135	2500
295	91	185	3200

The increase from 2500 to 3200 calories may be made by rearrangement of foods in

the diet without much increase in the bulk. A diet of 3200 calories is unquestionably ample enough to permit gain in weight in all instances. In some instances dietetic instructions in a high protein high vitamin diet with instructions to begin with a diet valued at 1300 calories and to increase the diet each week by an addition of 300 calories until a diet containing 3200 calories has been reached has proved successful when carried out in the patient's home.

In most cases it is important for the physician to see the patient every day until she has developed enough confidence to overcome the aversion to food which previously had been the dominating factor militating against her recovery.

When cachexia is extreme treatment must be cautious and undertaken with the understanding that little or no improvement can be expected for some time. Aggressive treatment of patients who have extreme degrees of emaciation may prove disastrous. The necessity for tube feeding or for daily intravenous administration of fluid is a sign of danger and in such cases treatment should proceed with caution.

MANAGEMENT OF ACCOMPANYING CONDITIONS AND SUPPORTIVE MEASURES The finding of a relative degree of lymphocytosis is common in cases of anorexia nervosa and should cause no concern. It may be related to depressed function of the adrenal cortex. The return to normal may occur early during treatment. Likewise leukopenia is a common finding and the leukocytes in certain instances may be found sufficiently low in number to cause concern. This finding also has been found not to be of significance and the return to normal occurs later during recovery.

Anemia is not an uncommon finding and in rare instances may be severe. During treatment of the anorexia the anemia may be found to increase or appear for the first time secondary to retention of fluid as a consequence of treatment. The administration of 0.3 gm of ferrous sulfate after each meal is indicated when anemia is found. Transfusions are rarely indicated and only when the anemia is severe.

Pitting edema of the ankles or in some instances generalized edema may occur concomitantly with a gain in weight of as much

as 15 lbs (6.8 kg) during the first 2 weeks of treatment. Both of these are due to a retention of fluid as a result of a successful increase in the diet and do not signify cardiac or renal failure. The edema may persist for from several weeks to 2 months or longer. After the original gain in weight there may be no gain for several weeks or longer; however, observation of the patient will show unquestioned and progressive improvement. The weight curve may be misleading if used as a basis for the actual storage of flesh. With the gradual disappearance of edema the weight of water lost may be approximately equal to the weight of the flesh gained. At the end of the period during which water is lost the patient will show a progressive gain in weight.

During the first few weeks 30 mg of phenobarbital given two or three times a day and 10 drops of tincture of belladonna in $\frac{1}{2}$ glass of water 20 minutes before meals

patient
in the
-cretory

urogram as renal calculi have been found in a number of instances. These patients drink very little fluid and as a result the urinary output is markedly decreased. Some of them probably because of a negative nitrogen balance have a tendency to osteoporosis and consequently excrete excessive amounts of calcium in the urine. All of these factors favor the formation of stones in the urinary tract.

Patients should be warned against falling. Osteoporosis in some instances may be marked. I have seen several severe fractures occurring in these patients as the result of a minor fall during treatment.

As a rule to patients who are seen after many months of inanition associated with amenorrhea estrogens may be administered cyclically 3 weeks out of 4. Doses of 0.5 mg of diethylstilbestrol daily by mouth may be used. This is done to aid in priming the uterus for subsequent return to ovarian function and to shorten the period of marked atrophy often seen in these cases. Usually approximately 6 months is required for these patients to regain their standard weights; however, in some instances the return of the normal menstrual cycle may require a much longer period.

It is surprising that these patients are exceptionally free from infections that terminate chronic debilitating diseases. In fact it is unusual to find them suffering from any complicating disease.

JOHN M. BERKMAN

REFERENCES

- Berkman J. M., Weir J. F. and Kepler E. J. Cal Observations on Starvation Edema Serum Protein and Effect of Forced Feeding in Anorexia. *Bull. N. Y. Acad. Med.* 1948.
- Edmondson J. Partial Starvation and Its Treatment. *Lancet* 1975 1945.
- Keys A. et al. Famine Edema and Mechanism of Its Formation. *Science* 103 669 1948.
- Pollack H. Letter to the Editor. *Nutrition Reviews* 4 84 1948.

NUTRITIONAL EDEMA

Nutritional edema (famine edema) can no longer be considered as a simple manifestation of protein deficiency; instead it is a complex phenomenon.

plasma protein this is not an invariable rule and even when hypoproteinemia is present the decrease may be but slight. Renal or cardiac failure is not a necessary part of the picture of famine edema.

The treatment of famine edema is essentially the treatment of semistarvation. Absolute bed rest is essential for the very ill with restricted ambulation for the less severely ill. Orally administered nutrients are preferable to parenteral alimentation. It is important not to overfeed patients during the first few days of re-alimentation. More than small amounts of fat are not well tolerated in the initial diet.

One of the most valuable therapeutic agents for initial refeeding of severely starved patients is dried skim milk. The experience during World War II provided no basis for belief that protein hydrolysates ad-

parenterally to individuals with nutritional edema is not to be recommended as there is danger of producing circulatory failure by the sudden administration of large quantities of parenteral fluid. These patients will usually tolerate reasonable quantities of protein orally. If however the serum protein levels are considerably reduced the cautious administration of salt free human plasma albumin serves to increase the serum protein concentration and usually results in a diuresis with resultant loss of tissue fluid.

The moderately and less severely ill cases of nutritional edema are best treated by a diet low in fat and composed of simple foods high in protein of good biologic value. Such foods are milk, eggs and meat. In addition the diet should contain cereals and fresh fruit. Initially the daily diet should contain 200 or 300 calories more than the intake level of the patient for the period immediately preceding therapy. The quantity of diet should be gradually increased by increments of 100 to 300 calories each 1 to 3 days as tolerated by the patient. It is essential to adjust the diet of the patient to his tolerance. Even in severe cases within 2 to 4 weeks after the institution of therapy the patient can usually tolerate 3000 to 4000 calories without gastric discomfort or vomiting.

Inasmuch as these patients seldom present evidence of specific nutritional deficiencies other than calories and protein it is usually unnecessary to administer supplementary vitamins. In occasional instances however pigmentation of the skin and glossitis may be relieved by the addition of supplementary niacin in moderate doses of 50 to 100 mg per day. The moderate anemia which frequently accompanies starvation does not respond to liver extract or iron. Mercurial diuretics or digitalis are not needed unless cardiac failure exists.

The general care of such patients includes the control of intercurrent infection with sulfonamides or antibiotics, protection from cold and chilling to which such patients are particularly sensitive and sympathetic nursing.

WILLIAM J. DARBY

DISEASES OF THE DIGESTIVE TRACT

DISEASES OF THE MOUTH, ESOPHAGUS, AND STOMACH

VINCENT'S ANGINA

(Trench Mouth Fusospirochloa Ulceromem-
branous Stomatitis)

This mildly contagious disease of the mucosa is usually confined to the tonsils, but sometimes affects the pharynx, mouth, gums, and even the larynx and trachea. During World War II a large number of cases were seen and gave ample opportunity for the use of the newer antibiotics. Comparison with the older drugs showed that arsenic in its various forms, chromic acid, gentian violet, and other such drugs in popular usage are definitely less effective than penicillin or the sulfonamides.

Penicillin produces a quick response and symptomatic cure. It may be used locally in the form of pastilles or lozenges, each containing 5000 units of penicillin, or it may be administered parenterally. In treating over 400 cases in the Navy, Strong and Willett sprayed the mouth with penicillin solution (250 units per cubic centimeter) and then prescribed penicillin lozenges to be dissolved in the mouth at hourly intervals. This procedure was carried out daily for 2 or more days. It was found that smears became negative in from 48 to 120 hours, while symptoms were relieved in 24 hours.

In severe cases the parenteral use of penicillin is preferred, 20,000 units being given every 3 hours to a total of 100,000 units. In patients not hospitalized, long-acting penicillin in a dosage of 300,000 units daily for 3 days may be used.

Sulfonamides. In 1945 Manson and Craig treated 48 cases of Vincent's angina with 0.5 gm sulfathiazole tablets orally. The symptoms disappeared in 24 hours, but they continued treatment for another 72 hours. In Wolfman's series of 61 Army Air Corps cases,

41 were treated with sulfadiazine or sulfathiazole, the daily dose being 6 gm, and the total dose per patient being 12 to 38 gm. In 78 per cent of these patients, the lesions healed in less than 20 days, but in the control series, treated with chromic acid, gentian violet, neoarsphenamine, or mapharsen, and locally with glycerine or with vitamin supplements, only 25 per cent of the patients had their lesions healed in less than 20 days.

Other Drugs. W. M. Johnson used nicotinic acid (niacin) systemically, and found that his patients were relieved of symptoms in about a week. To adults he gave 50 mg three times daily, and to children 10 to 50 mg three times daily, depending on the age of the child.

In the routine treatment of soldiers suffering from Vincent's angina, Kent advised the use of ascorbic acid (vitamin C) and recommended 0.6 gm daily for the first week, and 0.3 gm daily thereafter.

Local treatment to rid the mouth of the necrotic membrane consists of the use of hydrogen peroxide as a mouth wash. This should be done every 3 or 4 hours, the disinfectant being used in full strength or diluted one half. Relief is also given by sodium perborate used as a paste with cotton applicators or as a mouth wash.

Oral hygiene and prophylaxis and the removal of calculi and periodontal pockets are of the greatest importance in both acute and chronic cases.

ARTHUR E. MAHLE

REFERENCES

- Correspondence: Nicotinic Acid in Vincent's Angina. *JAMA*, 129:91, 1945.
Kent, B. S. Necrotic Gingivitis. *Lancet*, 1:642, 1943.
Manson, W. W., and Craig, I. T. Treatment of Vincent's Angina with Sulfathiazole. *JAMA*, 127:277, 1945.

Strong L W Jr and Willett E W Penicillin
Lozenges in Treatment of Vincent's Stomatitis
U S Nav M Bull 46 953 1946
Wolfram J Sulphonamide Therapy of Vincent's
Ang na Texas State J Med 42 26 1946

STOMATITIS

Knowledge of the causes of inflammation of the oral mucous membrane stomatitis has advanced so much in recent years that treatment now follows etiologic lines rather than those based on an outdated descriptive classification. The physiologic and pathologic state of this membrane depends either on local insult or on response to some systemic pathologic agent or disease. Local trauma includes reactions to heat and to chemicals as well as the closely related reactions to bacterial and mycotic infections and to viruses. Systemic diseases producing oral lesions include the blood diseases such as agranulocytic angina leukemia purpura and pernicious anemia the deficiency diseases such as sprue beriberi and pellagra and those conditions characterized by severe diarrhea. Many of these diseases will be discussed elsewhere only a few being considered here.

Recurrent and Mucous (peradenitis mucosa necrotica recurrens) should be grouped together since they all respond equally well to the same treatment.

Van Rooyen and Rhodes report that vesicle fluid from all varieties of herpetic eruptions can be inoculated into human skin with consequent production of a typical crop of simplex vesicles and that when the antibody content of serum of individuals subject to

recurrent lesions can be accomplished by using the patient's own vesicular fluid or as suggested by Foster and Abshuer by repeated vaccination. Woodburne advocates repeated vaccination with smallpox vaccine at 1 to 2 week intervals unless a "take" occurs in which case the reaction is allowed to subside before further vaccination.

Local treatment consists in the use of

mouth washes of dilute sodium perborate or hydrogen peroxide. In infants the mouth may be cleansed with these solutions. In chronic recurrent herpetic stomatitis a silver nitrate stick applied to the base of the ulcer has been used effectively.

Gangrenous Stomatitis (Noma Can crum Oris). Most authors are of the opinion that there is no specific treatment for gangrenous stomatitis (Wang Sung and Sung) but that early diagnosis and prompt measures to improve the nutritional state of the patient are essential. Agnew advises the use of massive multivitamin therapy especially vitamins A B complex, C and D and in addition a high caloric high protein and high vitamin diet.

Wang Sung and Sung advise against surgical excision but they do advise removal of necrotic tissue irrigation of the mouth with 1:1000 potassium permanganate solution twice daily and a warm saline solution rinse every 30 minutes. In addition blood transfusions are given to patients seriously ill. Agnew believes in excision into healthy tissue by electrocautery.

Favorable results have followed the use of a 1 to 4 day treatment with sulfathiazole or sulfadiazine in single doses of from 0.9 gm to 4.00 gm with a total dosage of from 4.5 gm to 18 gm daily.

Dawson combines the use of penicillin

Stomatitis Following the Use of Penicillin. Streptomycin and the Sulfonamides. Since the advent of these drugs stomatitis has been seen in association with their administration. It has been noted that penicillin administered orally has been more prone to produce stomatitis than that given parenterally, and it is the general opinion that the parenteral use in itself does not produce oral lesions. Ellinger and Shattock have noted that penicillin treated patients may develop a stomatitis involving the entire mouth—tongue cheeks and palate—with the mucous membrane becoming red tender and edematous. In such patients they were able to demonstrate a nicotinamide deficiency, the degree depending upon the relative effect on intestinal flora. Daily urinary nicotina

made was determined before during and after oral administration of penicillin. Oral lesions appeared within 3 to 4 days following therapy and after the sixth day the patient became forgetful and experienced difficulty in maintaining equilibrium. These authors also noted similar symptoms in some patients after sulfadiazine therapy. They advise the use of nicotinic acid 100 mg daily given either orally or parenterally to any individual maintained on oral penicillin.

Phillips reports 5 patients receiving oral penicillin who after 24 hours developed a burning sensation in the mouth and throat and a soreness of the gums together with aphthous like lesions which ulcerated leaving a dirty gray base. The tongue became beefy red and painful.

The author has seen painful stomatitis with a beefy red tongue and red buccal mucous membrane following the use of penicillin orally by inhalation.

Beham and Ferr report the occurrence of painful stomatitis of the aphthous variety developing during streptomycin treatment of both pulmonary and extrapulmonary tuberculosis. The lesion healed rapidly with discontinuance of the streptomycin only to reappear with resumption of the drug. He was unable to correlate the stomatitis with the daily or with the total amount given or with the duration of administration.

ARTHUR E. MAHLE

REFERENCES

- Agnew R G. *Cancer* *Ons J Periodont* 18 22 1947
 Beham H and Ferr H. Stomatitis due to Streptomycin. Report of 3 Cases. *JAMA* 138 495 1948
 Da son J. *Cancer* *Ons Brit Dent J* 79 151 1945
 Ellinger P and Shattock, F M. Nicotinic Deficiency after Oral Administration of Penicillin. *Brit M J* 2 611 1946
 Foster P D and Absher A H. Smallpox Vaccine in Treatment of Recurrent Herpes Simplex. *Arch Dermat & Syph* 36 994 1937
 Phillips E. Glossitis and Stomatitis due to Penicillin Lozenges and Troches. *Permanent Found M Bull* 4 90 1946
 Van Rooen C E and Rhodes A J. Herpes Febrilis in Virus Diseases of Man. Ed 2. New York: Thomas Nelson & Sons 1943 Ch 17
 Wang Sung C C and Sung R Y. Some Clinical Observations Concerning Noma. *Am J Orthodontics (Oral Surg Sect)* 33 284 1947

Woodburne A H. Herpetic Stomatitis (Aphthous Stomatitis). *Arch Dermat & Syph* 43 453 1941

ESOPHAGITIS

Esophagitis is probably the most common disease of the esophagus since it occurs in a large number of conditions. Because of its anatomic structure the esophagus is unusually vulnerable to pathogenic organisms from the oral cavity from regurgitated stomach contents and from intra abdominal infections passing through the blood stream and lymph channels.

Treatment should be directed toward the fundamental causes which can be classified as follows: (1) traumatic as after the frequent passage of stomach tubes after repeated vomiting after the drinking of escharotics, strong acids, alkalis and other poisons and after the swallowing of foreign bodies; (2) in association with severe infections and debilitating diseases; (3) in connection with abdominal diseases such as cholecystitis, duodenal ulcer and appendicitis; (4) in relation to certain abnormalities of the esophagus itself such as hiatal hernia, esophageal diverticula, cardiospasm and esophageal varices. Other diseases such as thrush, syphilis, tuberculosis and actinomycosis will be considered elsewhere.

In group 1 the simplest form of management is prevention i.e. care in the passage of stomach tubes, control of vomiting and prevention of the accidental swallowing of poisons and foreign bodies. But once acute esophagitis is established treatment is directed first to relief of pain by such measures as the application of an ice bag to the sternum and neck and the swallowing of ice in small bits held in the mouth. Tincture of belladonna 20 drops every 4 hours will relieve spasm. The diet is bland and the belladonna can be given 20 minutes before each feeding. Bastedo advises the use of an unsweetened lozenge containing 2 grains (0.13 gm) of ethyl aminobenzoate dissolved in the mouth to produce an anesthetic effect and to allay pain and spasm when food is swallowed. Small amounts of olive oil or milk every 3 to 4 hours give relief.

In esophagitis due to chemical trauma the same regimen can be followed but the esophagus should be put at rest by feeding

the patient with a duodenal tube kept in situ. In addition sedatives such as phenobarbital 30 mg three times daily should be used if the pain is severe and intravenous 5 per cent glucose should be administered as supportive treatment if there is definite dehydration.

In cases where the condition does not improve or where the acute condition has subsided particularly after the swallowing of chemicals it is well to study the esophagus roentgenologically in order to determine the amount of stenosis. In early cases it may be necessary to perform gastrostomy until the acute or subacute stage has subsided and scar tissue has formed. After stricture forms in cases following the drinking of escharotics graduated bougies should be passed after the patient has swallowed a guiding thread. In those cases too where there persists a good deal of esophageal spasm the passing of graduated bougies frequently gives relief. This can be said also of cases where ulcer forms. Barclay recommends the passage of bougies to stretch the base of the ulcer and finds that relief of symptoms and actual healing may follow such a procedure.

In group 2 treatment is naturally directed toward the underlying pathology. Esophagitis is frequently associated with debilitating conditions such as severe burns, diabetes mellitus, typhoid fever, arteriosclerosis, etc.

In group 3 treatment is likewise directed toward the intra-abdominal disease and the primary lesion—cholecystitis, duodenal ulcer or appendicitis—must be considered.

In group 4 where abnormalities of the esophagus precipitate the esophagitis certain conditions should be evaluated such as regurgitation of acid stomach contents, hiatal hernia, cardiospasm or the ulceration associated with esophageal varices in hepatic cirrhosis. The treatment of these conditions will be considered elsewhere.

ARTHUR E. MAHLE

PEPTIC ULCER OF THE ESOPHAGUS

Peptic ulcer of the esophagus as a primary entity is rare although esophagitis and peptic ulcer of the esophagus in association with certain anomalies are not too uncommon. In hiatal hernia particularly with a

congenitally short esophagus the occurrence of an ulcer between the esophageal and the gastric mucosa is not infrequent. In addition many patients give a history of previous gastric or duodenal ulcer or of cholecystitis. In such cases hematemesis may occur and may be severe.

Treatment in the early stages attempts to rest the esophagus and to prevent regurgitation of the acid stomach contents. The diet is that used in peptic ulcer except that the feedings may be larger and less frequent. One follows the usual Sippy treatment beginning with liquids and later adding more solid foods to the diet but keeping it bland. Alkalis and antacids such as aluminum hydroxide gel are given between feedings and some advise the use of olive oil or the sucking of bismuth lozenges. Belladonna 20 drops of the tincture or atropine $\frac{1}{100}$ grain (0.6 mg) by hypodermic may relieve spasm.

If the dysphagia persists and is marked and if on fluoroscopic examination with barium the esophagus shows considerable spasm dilatation with graduated bougies may give relief. Gastrostomy or jejunostomy has been performed in some intractable cases.

In a case reported by Morton and Brunschwig observed over a 10 year period gastrostomy was performed because of com-

a duodenal ulcer was found but no change in the roentgenologic picture was noted.

Ruptures of a peptic ulcer of the esophagus have not infrequently been reported with a resulting high mortality. Freisfel reports such a case with rupture into the mediastinum but with recovery.

In summary peptic ulcer of the esophagus should be treated medically by diet, antacids, antispasmodics and rest. If this regimen gives no relief and if dysphagia and spasm of the lower esophagus are demon-

with the aid of a previously swallowed guide thread. Satisfactory results are obtained with bougies graduated from No. 27 to No. 45. French Gastrostomy and jejunostomy are rarely necessary.

ARTHUR E. MAHLE

- Barclay, A E *The Digestive Tract, A Radiological Study of its Anatomy Physiology and Pathology* Cambridge England University Press 1933
- Bastedo W A Friedenwald J and Soper H W Symposium on Management of Oesophagitis *Am J Digest Dis*, 2:379 1935

- Morton, D R, and Brunschwig A Peptic Ulcer of Esophagus Report of Patient with 10 Year Follow up *Gastroenterology* 7:314 1948
- Preskel, E Peptic Esophageal Ulcer Non-fatal Perforation *Lancet*, 1:497, 1946
- Vinson, P P and Butt, H R Esophagitis Clinical Study *JAMA*, 106:994, 1938

FUNCTIONAL INDIGESTION

CARDIOSPASM

Cardiospasm may be mild, when the symptoms are chiefly pain, moderate dysphagia, and regurgitation or more advanced, with marked dysphagia, regurgitation, vomiting and pain the latter rather moderate in severity. In the milder cases there is but little weight loss and nutrition is only slightly impaired, but in the severe cases the weight loss is marked there is emaciation with dehydration and the symptoms are of long duration. On ingestion of barium these patients are found to have a smooth obstruction at the cardia, moderate to marked dilatation of the esophagus above the obstruction, and frequently a marked tortuosity of the esophagus.

Treatment of cardiospasm is threefold (1) medical, (2) mechanical (dilatation of the esophagus) (3) operative (Vinson).

Medical Therapy The drugs used in treatment are those employed to relieve spasm of the cardia of the esophagus. Vinson found that the use of tincture of belladonna in doses of 20 drops brought only temporary relief. This is also true of hypodermic injections of atropine 0.4 mg to 0.6 mg, and after long usage the drug may have to be increased to as much as 15 mg before eating. Robinson and Wilkinson were able to relieve cardiospasm at first with the use of octyl nitrite (the nitroso ester of 2 ethyl n hexyl nitrite) in 3 minim ampules, broken in a handkerchief and inhaled. As tolerance to the drug developed, its effectiveness was lost. To date, drug therapy has failed to relieve true cardiospasm with any degree of permanency, and this failure has resulted in the employment of mechanical and operative measures to relieve symptoms.

Mechanical Therapy The great majority of patients suffering from cardiospasm can

be treated successfully by dilatation. Petersen states that in 95 per cent of cases the disease can be cured by hydrostatic dilatation. Clagett and his co-workers state that 70 per cent of patients with cardiospasm can be completely relieved by one course of treatment with the hydrostatic dilator. In 30 per cent there is a tendency to recurrence which may take place at any time, immediately after treatment or as long as 25 years later. When there is recurrence the majority of patients can be relieved by subsequent dilatation. In approximately 2 to 5 per cent of patients dilatation has not proved efficacious, and here surgical intervention is indicated.

The method of dilating the cardia by hydrostatic pressure, as used by Vinson, Moersch, and others, was devised by Russell and improved by Plummer. This method is ably described by Vinson. The patient is instructed to swallow a silk twist thread usually about 5 yards long until the thread engages itself firmly in the loops of the intestines and is thus anchored. The thread can be started the evening before the contemplated dilatation, the patient being directed to swallow about 1 ft an hour.

The dilatation procedure is as follows: A No. 45 French olive is threaded upon the silk thread and guided down the esophagus. This is followed at once by a No. 60 French olive, likewise passed through the cardia. Many patients with mild cardiospasm will gain relief from this procedure alone or will gain temporary relief for some months, after which repetition of the passage of the sound may be done. This is particularly advisable in elderly patients.

If relief is not obtained by passage of a No. 60 French bougie or if the dilatation is so marked that it is obvious that such a procedure may not be of benefit, the hydro-

static bag is then introduced. This procedure is usually carried out about a week after the passage of the No. 60 French olive. The hydrostatic bag is introduced over the thread into the cardia to the most dependent portion of the esophagus. Then the thread is pulled taut and the dilator advanced to the correct depth so that the center of the dilator lies in the cardia. It is then held in place and distended with water until the gauge registers a pressure of 22 to 24 ft. of water. If the dilator has properly engaged the constriction at the cardia, the patient will experience severe pain as the dilator expands. Occasionally the dilator slips out of the narrowed cardia usually into the stomach but after a small amount of water is released the bag can again be pulled into the cardia and the dilatation resumed. This procedure is carried out by Vinson is done without anesthesia or the use of fluoroscopy for he feels that the handicap of attempting dilatation in the dark is greater than the advantage gained by visualizing the dilator in the cardia.

Complications of this procedure as in any type of instrumentation of the esophagus include perforation with resulting mediastinitis usually fatal. However since 1925 Vinson has had no fatal outcome in the more than 450 patients upon whom he has performed hydrostatic dilatation and he is of the opinion that the preliminary passage of the No. 60 French olive prevents overdistention if the hydrostatic bag alone is used in the preliminary dilatation.

In some methods for dilating the cardia air is used instead of water. Such an apparatus has been devised by Sippy, Einhorn and others. The dilating bag is passed in the usual manner and inflated by means of a sphygmomanometer bulb to the necessary pressure and diameter.

In 1913 and 1929 Hurst devised rubber tubes of $\frac{1}{8}$ to $\frac{1}{4}$ inch in diameter.

31 in. in length each containing the same weight of mercury (1 lb. 8 oz.). In 1929 Hurst described his technic for the passage of such mercury bougies and advised that it was best to pass such a bougie during the roentgen examination and to mark the bougie at the level of the incisor teeth with

the lower end extended 2 in. within the stomach. Successively larger bougies are passed the patients being taught to pass

after a week or if relief is not yet attained the bougie can be passed at intervals of every other day to a week. On several occasions the author has used a No. 60 French mercury bougie for mild cardiospasm in place of the No. 60 French bougie and secured relief in selected cases. In advanced cardiospasm Hurst advises the use of the Plummer hydrostatic bag because the mercury tube will curl up in the lower esophagus and not pass through the cardia into the stomach.

Operative Treatment. Of the operative measures used, simple gastrostomy alone is the procedure of choice and by this means the patient is fed with a gastrostomy tube. This does not relieve the primary obstruction although it may save the patient's life. When it has served its purpose, other means of relieving the cardia obstruction should be employed.

When the stomach has to be opened for the purpose of feeding, Vinson advises the manual dilatation of the cardia through the gastrostomy and finds that a previously swallowed thread is helpful in locating the cardiac opening. In 2 of his cases where angulation of the esophagus prevented introduction of a dilator into the cardia, this type of manual dilatation was quite satisfactory.

Sympathectomy operations on the cardiac sphincter, removal of abdominal sympathetic ganglia and removal of the cervical sympathetic ganglia have all been performed with but little benefit.

Recently there have been reports of intractable cardiospasm treated successfully by esophagogastrostomy. Clagett, Moersch and Fischer reported 4 patients successfully so treated. Good functional results were obtained but the dilated esophagus did not appear to reduce appreciably in size following the operation. In reviewing the literature these authors came to the conclusion that the transperitoneal route carried a lower operative mortality than the transpleural route. The 4 cases reported were patients with long standing cardiospasm in whom

dilatation of the cardia had failed to produce more than temporary relief

Peterson reports 10 cases operated upon for marked cardiospasm esophagogastrotomy being performed in 8 by the trans pleural route and in one by the abdominal route. He is of the opinion that the procedure is a safe one and is a means of providing relief of symptoms in cardiospasm.

ARTHUR E. MAHLE

REFERENCES

- Clagett O T Moersch H J and Fischer A Esophagogastrotomy in Treatment of Cardiospasm *Surg Gynec & Obst* 81:440 1945
 Hertz A F Achalasia of the Cardia. *Quart J Med* 8:300 1914 15
 Hurst A F and Rake G W Achalasia of the Cardia (So-called Cardiospasm) *Quart J Med* 23:491 1930
 Peterson F R Transpleural Esophagogastrotomy in Treatment of Cardiospasm *Tr West S A* (1945) 53:108 1946
 Robson T and Wilkinson R S Tolerance to Octyl Nitrite in Achalasia of the Cardia *Lancet* 1:737 1946
 Vinson P P Diagnosis and Treatment of Cardiospasm *South M J* 40:387 1947
 Vinson P P *Diagnosis and Treatment of Diseases of the Esophagus* Springfield Ill C C Thomas 1940

PYLOROSPASM

As the term signifies pylorospasm is defined as spasm of the pyloric muscle. In infants it is closely related to pyloric stenosis and must be considered in the differential

and usually associated with hypertrophic antral gastritis. In pylorospasm from extragastric lesions one must consider cholecystitis, appendicitis, pancreatitis and diseases of the urinary tract. The condition also occurs in certain neurogenic and psychoneurotic states among which are included migraine, anorexia nervosa and other emotional states. The projectile vomiting related to intracranial pressure from brain tumor can be considered a reflex pylorospasm.

Treatment should be directed to the underlying disease. For in adults pylorospasm is merely a symptom in differential diagnosis and not a disease in itself.

In peptic ulcer the therapy is obvious and where there is pylorospasm without sign of gastric retention medical management of the ulcer should be instituted. But in hypertrophic antral gastritis surgical treatment should not be delayed in those doubtful cases where differentiation from cancer is difficult. Despite the combined clinical roentgenologic and gastroscopic examination of such patients there is error of diagnosis in about 20 per cent of cases.

In the second group that of cases related to functional and to extragastric organic disease—to brain tumor, cholecystitis and emotional states—therapy should be directed toward appreciation of the basic disturbance.

During the time the patient is undergoing various examinations to determine the cause of the pylorospasm symptomatic therapy is indicated. The use of a bland diet with 10 drops of tincture of belladonna and 30 mg of phenobarbital before each meal often provides temporary relief of discomfort.

ARTHUR E. MAHLE

HYPERCHLORHYDRIA AND HYPOCHLORHYDRIA

Any discussion of the therapy of hyperchlorhydria or hypochlorhydria immediately introduces the question of what constitutes normal gastric acidity and what if any symptoms an abnormal acidity can be expected to produce. A great deal of experimental work has been done on the relationship of gastric acidity to the total gastric secretion and on the importance of the secretion of mucus, pepsin, etc. Next to be evaluated is the influence of intrinsic and extrinsic factors on gastric secretion and the effect of certain drugs and chemicals the stimulating effect of histamine, the inhibiting action of urogastrone, the neutralizing action of the antacids and the buffer action of milk and cream on neutralization—all must be considered.

Hyperchlorhydria. Some patients with excessive acidity get relief from the use of antacids such as aluminum hydroxide preparations but the interesting point is that

many of these patients seem to experience relief merely because of the eructation of the gas which so frequently follows the taking of antacids. Two ounces each of milk and cream will frequently relieve the symptoms of excessive acid secretion.

— evidence
is low
ls show

no symptoms of intestinal disturbance any more than do those whose acidity is abnormally high.

It is perfectly simple to augment gastric secretion with hydrochloric acid and it is generally accepted that some older patients with hypochlorhydria have vague gastro intestinal symptoms even disturbing diarrhea which are relieved with the ingestion of 4 cc of dilute hydrochloric acid with meals. The acid should be taken through a glass drinking tube to avoid injury to the enamel of the teeth. A proprietary preparation called acidulin may be taken in tablet form 1 tablet with each meal in place of the liquid hydrochloric acid.

In summary hyperchlorhydria and hypochlorhydria are in themselves not important causes of symptoms but result from many factors both intrinsic and extrinsic and should so be considered and treated.

ARTHUR E. MAHLE

GASTRITIS

Acute Gastritis. Acute inflammation of the stomach may be provoked by abuse and injury from irritating food or drink such as strong spices, alcohol, coarse fibers, seeds or skins from corrosive chemicals or drugs or from hematogenic invasion by bacteria. Depending on the kind and source of the insult the inflammatory reaction may be hyperemia, congestion, edema, hemorrhage, erosive ulceration, suppuration or abscess.

ACUTE SIMPLE EXOGENOUS GASTRITIS. This condition is caused by overindulgence in quantity or to poor quality of food or liquid and consequent irritation of the gastric mucosa. The condition is commonly self treated and transient. Physical discomfort comprises nausea, vomiting, anorexia and abdominal distress. Occasionally the lower intestinal tract may be affected with resultant crampy diarrhea. When symptoms do not subside

promptly with home remedies, medical attention is sought.

If nausea and vomiting persist the stom-

liquids often subdue the nausea. Absorbent substances such as dry salted toast, puffed rice or salted soda crackers may be more acceptable than liquids. Citrate of magnesia may be advisable to clear the bowel or a warm enema to quiet the colon. Effervescent bromide mixture gives helpful sedation. Generally opiates are not well tolerated but 30 mg of codeine and 0.4 mg of atropine may be given hypodermically if required. After fasting for 24 to 48 hours warm liquids are taken. Soft and then semisolid foods are added gradually until the resumption of the usual diet within 4 or 5 days.

ACUTE CORROSIVE GASTRITIS. This form of gastritis results from deliberate or accidental swallowing of poison, strong chemical solution or excessive amount of a drug. Gastric symptoms are apt to be more severe than those of simple gastritis and may include systemic signs according to the nature and action of the substance ingested. Stomach washing is usually necessary. The following solutions are suggested for lavage of the stomach.

For Strong Acids. Large quantities of fluids for dilution solutions may contain 2 oz of milk of magnesia or 8 gm of soda bicarbonate or plain soap suds.

For Oxalic Acid. Solutions of calcium and magnesium bases.

For Alkalis. Weak acids: lemon juice, dilute vinegar.

For Phenol. Sodium sulfate 15 gm in 500 cc water.

For Iodine. Starch solution.

For Mercury. Wash the stomach with water, then egg and milk. Prune consideration is prevention of renal damage.

For Silver Nitrate. Plain table salt.

For Zinc Salts. Sodium or potassium carbonate.

1 OZ. LIME JUICE AND 2 OZ. SODIUM CARBONATE in a glass of water. Saline or castor oil purge is advisable.

For Tartar Emetic Alkali strong tea or tannic acid solutions

For Lead Sulfates of magnesium and sodium

For Copper Salts Potassium ferrocyanide 1 teaspoonful in a glass of water

When systemic effects are anticipated saline or castor oil catharsis is indicated Subsequent treatment of the gastritis is that described for exogenous gastritis

ACUTE HEMATOGENOUS GASTRITIS Infectious diseases such as diphtheria influenza meningitis pneumonia and others may result in acute hemogenous gastritis Measures to relieve associated gastrointestinal discomforts are ordinarily incorporated in the management of acute epidemic and infectious diseases If the febrile illness is protracted vitamins and minerals should be supplemented to prevent development of simple inflammation into a chronic deficiency or degenerative form of gastritis

ACUTE PILEGMOUS GASTRITIS Suppuration of the stomach wall may result from trauma malignant or ulcerous gastric abscess or staphylococcal streptococcal pneumococcal or *E. coli* or typhoid bacteremia Treatment of the primary disease may suffice for the gastric condition but full use of sulfonamides and penicillin as indicated should be assured Gastric resection may be required

Chronic Gastritis Chronic gastritis has been accepted as an inflammatory or degenerative disease of the stomach on the basis of related roentgenographic gastroscopic and histologic demonstrations of changes in the gastric mucosa and wall Causes for acute gastritis are usually apparent etiology of chronic gastritis is except in a few instances unknown

Inherent capability of an objectively abnormal gastric mucosa to evoke subjective symptoms is questionable The lining of the stomach may appear normal atrophic or hypertrophic with no declared gastric distress Heartache backache weakness fatigue insomnia anorexia and similar psychosomatic complaints may not invariably be attributed to the stomach When the gastric mucosa in any state normal atrophic or hypertrophic becomes hyperemic congested edematous eroded or ulcerated uncomfortable or painful sensations may be

aroused A normal stomach is sensitive only to stress and tension of the entire wall Presumptively, subjective symptoms arise when tissues of the mucosa submucosa muscle layer or serosa are disordered and responses to stimuli of contraction or stretching are enhanced Aberrations of secretion seldom provoke notable sensations Treatment of chronic gastritis is based on these considerations and for practical purposes may be discussed as recurrent superficial gastritis atrophic gastritis hypertrophic gastritis and gastritis of the postoperative stomach

RECURRENT OR CHRONIC SUPERFICIAL GASTRITIS This form of gastritis may eventuate in atrophy of the gastric mucosa The condition occurs in stomachs that are apparently susceptible to slight insults The gastric mucosa is hyperemic congested edematous hemorrhagic often with aphthae or superficial erosions and mucopurulent exudate The symptoms are epigastric pressure distress after eating nausea and anorexia

A therapeutic regimen comprises rest construed as relief from duties and physical activities liquid semisolid or soft diet indicated daily maternal glass of warm water

or glabra absorb or aluminum gels 4 cc of dilute hydrochloric acid with meals when gastric secretions are anacid 30 mg of phenobarbital and 0.4 mg of atropine sulfate may be given for hypertonicity or hypersecretion Constipation should be corrected by diet and bowel training Good mastication should be assured by adequate dentures oral sepsis and sinus discharges should be eradicated When exacerbations have subsided instructions should be given to regulate eating habits to moderate use of condiments to bacco and alcohol to avoid physical fatigue or mental stress and to have proper care of febrile infectious illnesses

ATROPHIC GASTRITIS Atrophy of the gastric mucosa is readily recognized as patchy or diffuse involvement but does not always appear inflammatory That is in some instances the condition presents the aspect of primarily faulty or defective morphologic fabrication or of concurrent deficiency of elements for cell growth In other cases

evidences of quiescent or active inflammation are seen. With either state, manifestations of hyperplasia and regeneration may be discernible. The designation of gastritis may not be universally applicable to all gastric mucosal atrophy.

Atrophy of the gastric mucosa may be associated with achlorhydria, anemia, gastric polyps, or cancer, and these ancillary disorders may be productive of the symptoms in particular cases. Simple, disassociated gastric atrophy or atrophic gastritis may not incite notable subjective discomfort. Consequently, therapy is frequently directed to correction of anemia by iron liver extract, folic acid or vitamins—usually B complex—as indicated, or to stopping achylia diarrhea by dilute hydrochloric acid, or to extirpation of neoplasms. Dilute hydrochloric acid is used in amounts of 10 to 30 drops in a wineglass of water, to be sipped with meals. For microcytic hypochromic anemia, 10 grains (0.65 gm.) of ferrous sulfate are given with each meal. For pernicious anemia, concentrated liver extract is injected intra-

be bland and smooth without coarse or irritating food substances, and arranged as four or five daily meals. The diet may be augmented by mixtures of concentrated protein, minerals and vitamins such as meretene. Good dentures are essential to assure proper mastication. Oral sepsis and nasopharyngeal discharges should be eradicated. Alcoholic beverages are usually not well tolerated, but occasionally wine before meals will arouse the appetite.

HYPERTROPHIC GASTRITIS. Roentgeno-

hyperactive peristalsis and pylorospasm with protrusion of redundant membrane into the base of the duodenal bulb. When these phenomena are also seen through the gastroscope, with superficial erosion and ulceration, submucosal hemorrhage, edema, and exudate, the condition may be properly

designated as inflammation that is, hypertrophic gastritis. When the changes described are observed in the stomach, subjective symptoms may be expected. Abdominal complaints in a case of indubitable hypertrophic gastritis are similar to those induced by peptic ulcer, except that epigastric distress may be felt immediately after eating, and pain experienced when the stomach is empty is not readily relieved by ingesta. Nausea and vomiting are common, but nocturnal discomfort is rare. The epigastric pain is diffuse and does not radiate.

arranged in three approximately equal amounts of food supplemented with feedings between meals. A glass of hot water with a pinch of salt, or carbonated alkaline water such as Vichy, or hot weak tea taken on arising may wash away or dilute accumulated night secretions. A sedative antispasmodic mixture, such as a tablet of 30 mg ($\frac{1}{4}$ grain) phenobarbital with 7.5 mg ($\frac{1}{8}$ grain) extract of belladonna may be beneficial, given at 11 A.M., 5 P.M., and at bedtime. Absorbents, as the aluminum gels, may be prescribed to be taken between meals, before or after the midday feedings, as indicated by the occurrence of pain. Liquid suspensions, 1 or 2 teaspoonfuls in $\frac{1}{2}$ glass of water, are better than tablets. Gastric lavage with weak solutions of peroxide or silver nitrate has been recommended, but is seldom necessary. Deep roentgen therapy has been used in severe and intractable hypertrophic gastritis, but is not advisable for the ordinary case, consequent atrophy and vascular damage may be more harmful than the mucosal hypertrophy.

GASTRITIS OF THE POSTOPERATIVE STOMACH

The gastric mucosa of a whole or resected stomach with a jejunostomy, is invariably inflamed. Congestion, hyperemia, edema, hemorrhage, erosion, ulceration, hypertrophy, and atrophy may exist in variable degrees. Slight alterations evoke no uncomfortable sensations. Symptoms due to immediate postprandial hyperglycemia or from late hypoglycemia may be abolished by adjustment of the food intake to frequent equal meals, balanced with respect to protein and carbohydrate.

For *Tartar Emetic* Alkali, strong tea, or tannic acid solutions

For *Lead* Sulfates of magnesium and sodium

For *Copper Salts* Potassium ferrocyanide, 1 teaspoonful in a glass of water

When systemic effects are anticipated, saline or castor oil catharsis is indicated. Subsequent treatment of the gastritis is that described for exogenous gastritis.

ACUTE HEMATOGENOUS GASTRITIS Infectious diseases such as diphtheria, influenza, meningitis, pneumonia and others may result in acute hematogenous gastritis. Measures to relieve associated gastro-intestinal discomforts are ordinarily incorporated in the management of acute epidemic and infectious diseases. If the febrile illness is protracted, vitamins and minerals should be supplemented to prevent development of simple inflammation into a chronic deficiency or degenerative form of gastritis.

ACUTE PHILEGMOUS GASTRITIS Suppuration of the stomach wall may result from trauma, malignant or ulcerous gastric abscess or staphylococcal, streptococcal, pneumococcal or *E. coli* or typhoid bacteremia. Treatment of the primary disease may suffice for the gastric condition, but full use of sulfonamides and penicillin as indicated should be assured. Gastric resection may be required.

Chronic Gastritis Chronic gastritis has been accepted as an inflammatory or degenerative disease of the stomach on the basis of related roentgenographic, gastroscopic, and histologic demonstrations of changes in the gastric mucosa and wall. Causes for acute gastritis are usually apparent, etiology of chronic gastritis is, except in a few instances, unknown.

Inherent capability of an objectively abnormal gastric mucosa to evoke subjective symptoms is questionable. The lining of the stomach may appear normal, atrophic, or hypertrophic with no declared gastric distress. Headache, backache, weakness, fatigue, insomnia, anorexia and similar psychosomatic complaints may not invariably be attributed to the stomach. When the gastric mucosa in any state, normal, atrophic, or hypertrophic becomes hyperemic, congested, edematous, eroded, or ulcerated, uncomfortable or painful sensations may be

aroused. A normal stomach is sensitive only to stress and tension of the entire wall. Presumptively, subjective symptoms arise when tissues of the mucosa, submucosa, muscle

provoke notable sensations. Treatment of chronic gastritis is based on these considerations and for practical purposes may be discussed as recurrent superficial gastritis, atrophic gastritis, hypertrophic gastritis and gastritis of the postoperative stomach.

RECURRENT OR CHRONIC SUPERFICIAL GASTRITIS This form of gastritis may eventuate in atrophy of the gastric mucosa. The condition occurs in stomachs that are apparently susceptible to slight results. The gastric mucosa is hyperemic, congested, edematous, hemorrhagic, often with aphthae or superficial erosions and mucopurulent exudate. The symptoms are epigastric pressure, distress after eating, nausea and anorexia.

A therapeutic regimen comprises rest, construed as relief from duties and physical activities, liquid, semisolid or soft diet is indicated, daily maternal glass of warm water with pinch of salt or soda bicarbonate or glass of alkaline water such as Vichy, absorbents between meals, such as kaolin or aluminum gels, 4 cc of dilute hydrochloric acid with meals when gastric secretions are anacid, 30 mg of phenobarbital

for bowel training. Good mastication should be assured by adequate dentures, oral sepsis and sinus discharges should be eradicated. When exacerbations have subsided, instructions should be given to regulate eating habits, to moderate use of condiments, to bacco, and alcohol, to avoid physical fatigue or mental stress, and to have proper care of febrile, infectious illnesses.

ATROPHIC GASTRITIS Atrophy of the gastric mucosa is readily recognized as patchy or diffuse involvement, but does not always appear inflammatory. That is, in some instances the condition presents the aspect of primarily faulty or defective morphologic fabrication, or of concurrent deficiency of elements for cell growth. In other cases

evidences of quiescent or active inflammation are seen. With either state, manifestations of hyperplasia and regeneration may be discernible. The designation of gastritis may not be universally applicable to all gastric mucosal atrophy.

Atrophy of the gastric mucosa may be associated with achlorhydria, anemia, gastric polyps, or cancer, and these ancillary disorders may be productive of the symptoms in particular cases. Simple, disassociated gastric atrophy or atrophic gastritis may not incite notable subjective discomfort.

complex—as indicated, or to stopping achylic diarrhea by dilute hydrochloric acid, or to extirpation of neoplasms. Dilute hydrochloric acid is used in amounts of 10 to 30 drops in a wineglass of water, to be sipped with

hemoglobin values and erythrocyte counts.

As part of medical treatment, diet should be bland and smooth, without coarse or irritating food substances, and arranged as four or five daily meals. The diet may be augmented by mixtures of concentrated protein, minerals, and vitamins such as meretene. Good dentures are essential to assure proper mastication. Oral sepsis and nasopharyngeal discharges should be eradicated. Alcoholic beverages are usually not well tolerated but occasionally wine before meals will arouse the appetite.

HYPERTROPHIC GASTRITIS Roentgeno

hyperactive peristalsis and pylorospasm with protrusion of redundant membrane into the base of the duodenal bulb. When these phenomena are also seen through the gastroscope, with superficial erosion and ulceration, submucosal hemorrhage, edema, and exudate, the condition may be properly

designated as inflammation, that is, hypertrophic gastritis. When the changes described are observed in the stomach, subjective symptoms may be expected. Abdominal complaints in a case of indubitable hypertrophic gastritis are similar to those induced by peptic ulcer, except that epigastric distress may be felt immediately after eating, and pain experienced when the stomach is empty is not readily relieved by ingesta. Nausea and vomiting are common, but nocturnal discomfort is rare. The epigastric pain is diffuse and does not radiate.

ings between meals. A glass of hot water with a pinch of salt, or carbonated alkaline water such as Vichy, or hot weak tea taken on arising, may wash away or dilute accumulated night secretions. A sedative antispasmodic mixture, such as a tablet of 30 mg ($\frac{1}{2}$ grain) phenobarbital with 75 mg ($\frac{3}{4}$ grain) extract of belladonna may be beneficial, given at 11 A.M., 5 P.M., and at bedtime. Absorbents, as the aluminum gels, may be prescribed to be taken between meals, before or after the midday feedings, as indicated by the occurrence of pain. Liquid suspensions, 1 or 2 teaspoonfuls in $\frac{1}{2}$ glass of water, are better than tablets. Gastric lavage with weak solutions of peroxide or silver nitrate has been recommended, but is seldom necessary. Deep roentgen therapy has been used in severe and intractable hypertrophic gastritis, but is not advisable for the ordinary case, consequent atrophy and vascular damage may be more harmful than the mucosal hypertrophy.

GASTRITIS OF THE POSTOPERATIVE STOMACH
The gastric mucosa of a whole or resected stomach, with a jejunostomy, is invariably inflamed. Congestion, hyperemia, edema, hemorrhage, erosion, ulceration, hypertrophy, and atrophy may exist in variable degrees. Slight alterations evoke no uncomfortable sensations. Symptoms due to immediate postprandial hyperglycemia or from late hypoglycemia may be abolished by adjustment of the food intake to frequent equal meals, balanced with respect to protein and carbohydrate.

SYPHILIS OF THE STOMACH, *gummatous* or diffusely infiltrative, is seldom symptomatic and, in any case, systemic antiluetic therapy suffices

Gastritis due to leukemia or lymphogranulomatous diseases or associated with uremia, acidosis, portal stasis, or cachexia requires no specific treatment

DIET SCHEDULE FOR CHRONIC GASTRITIS

Breakfast Fresh fruit juice, strained if necessary, or cooked fruit sauce, with no skin or seeds

Eggs, prepared in any manner, fat required should be butter or fresh bacon fat

Bacon crisp parts should be well masticated

Cereal farina, cream of wheat, corn meal, rolled oats cooked all night in double boiler. Whole milk or cream, and sugar

White or graham bread plain or toasted, with butter and jelly, or jam or preserves with no rind or seeds, or strained honey

French coffee (*café au lait*), warm milk and coffee, equal parts, weak coffee and cream, cocoa or weak chocolate, hot milk

Lunch and dinner Select foods and apportion quantities to make about two equal meals

Broth or bouillon for atrophic gastritis, perhaps not for hypertrophic gastritis

Cream soup, chowder thick strained pea, corn, bean, or lentil soup

Meat beef, mutton, lamb, chicken, fish, oysters, roasted, baked, or broiled

Potato white or sweet, baked, boiled or mashed

Macaroni, spaghetti, noodles, creamed or simply seasoned with strained tomato juice, boiled rice

Hominy, stewed tomatoes, strained, cauliflower, broccoli, asparagus tips, carrots, baked squash

If very young and tender, peas, lima beans, beets, green string beans. All vegetables well cooked, to consistency of mashed potato when crushed with fork, or pureed

Greens chopped in food mill or strained through coarse collander, spinach, chard, collards, kale, mustard, beet, and turnip

White or graham bread, plain or toasted, or crusty biscuits, butter, jelly, seedless and skinless jam or preserves

Cottage or cream cheese

Plain gelatin or jello may be used as salad with mayonnaise or French dressing, and tender leaf lettuce

Dessert Gelatin or jello, plain or flavored, soft, partially melted plain icecream, custards, pudding, blancmange and similar preparations, plain cake, fruit sauces with no skin or seed

Beverages as for breakfast, weak tea, buttermilk, fruit juice

Seasoning salt, and herbs as basil, marjoram, thyme, tarragon, parsley, sage, dill, chives, celery

Dried or powdered preparations are stronger than fresh herbs, but in any form, seasoning of

this kind should be added late in the cooking process. Several herbs blended are better than a single one used in quantity. Strong spices and condiments should not be used.

Good appetite is fostered by taste, and attention to what the French call *les fines herbes* will be appreciated and gratifying. When appetite is good, the diet is varied, and the quantity of food is adequate, supplementary minerals and vitamins are unnecessary.

When gain in weight is desirable, between meal feedings may be planned, consisting of milk or fruit juice with bread and butter or jelly sandwich, plain cake or sugar cookie, or similar articles from the food list. Milk may be complemented with one of several powder preparations of protein and carbohydrate, most of which are also fortified with vitamins. Meretene is satisfactory. The diet may be modified in fruit and vegetable content according to intestinal function.

JAMES B. CAREY

REFERENCES

- Bockus, H. L. *Gastroenterology*. Philadelphia: W. B. Saunders Company, 1943, Ch. XXI, p. 258.
 Carey, J. B. Diseases of the Mouth, Esophagus, Stomach and Duodenum, in *Outlines of Internal Medicine*. Edited by C. J. Watson. Dubuque, Iowa: William C. Brown Company, 1947.
 Schindler, R. *Gastritis*. New York: Grune & Stratton, 1947.

PEPTIC ULCER: GASTRIC AND DUODENAL

Therapeutics of simple, benign peptic ulcer comprises symptomatic, restorative, and, pre-eminently, preventive integrants. Complete and continuous abolition of pain is assurance that aggravating disturbance of secretory and motor functions of stomach and duodenum have been altered or controlled and conditions favorable for healing of an ulcer have been established. Peptic ulcers originate when the normal secretory, circulatory, and muscular activities of the stomach or duodenum are frequently and persistently deranged. Congestion, hyperemia, and engorgement from vasodilatation, or relative ischemia from vasoconstriction, concomitant with depressed formation of protective mucus, and accelerated production of juice with high acid and pepsin content, are conducive to ulceration of stomach

or duodenal mucosa. Hypertonicity and hypermotility contribute to the genesis of ulcer.

The first stage of an ulcer is circumscribed submucosal or mucosal hemorrhage. Many of these absorb, but others are eroded and digested by gastric juice, perhaps become infected, and a chronic ulcer is the consequence. The continuous corrosion and digestion by gastric juice promotes chronicity. The differences between gastric and duodenal ulcers are due to location and not to inherent peculiarities. As cause or effect, the volume of gastric secretion with duodenal ulcer is larger than normal, and the acid and pepsin content is greater. With gastric ulcer the stomach secretion may not be unusual in quantity or quality, but is none the less destructive to a vulnerable mucosa. The size of the duodenal ulcers is smaller than that of stomach ulcers. These circumstances are conditional on the incapacity of the diseased duodenal mucosa to produce the factors required properly to regulate gastric secretion and motility. With an ulcer in the stomach, the duodenum is presumptively normal and humoral reflexes are not interrupted or suppressed. The regularly alkaline duodenal content is also partially protective. Cancer does not occur in the first part of the duodenum frequently, and the rare instances noted in the duodenal loop have not been primarily ulcerous.

About 10 per cent of all individuals have, at some time, peptic ulcers. The first occurrence is likely to be during the course of, or following, an acute infectious disease, usually of the upper respiratory tract, or after sudden or continuous physical or mental strain. Recurrences, exacerbations, or complications are also initiated by any of these factors, or by gross indiscretions of diet. Original ulcers or early recurrences are prone to heal spontaneously or with simple measures such as rest, vacation, or regulation of diet.

Peptic Ulcers in Locations Other Than Stomach and Duodenum. Peptic ulcer may form in the lower esophagus, just above the opening into the stomach, presumably in gastric mucosa grown from the cardia. An ulcer rarely develops in the second part of the duodenum, with symptoms similar to those of the usual duodenal ulcer, except that nausea is common. Stenosis and perfora-

tion are infrequent, but hemorrhage may occur. Treatment is the same as for duodenal ulcer. Peptic ulcer may occur in aberrant gastric mucosa of a Meckel's diverticulum. Symptoms may be similar to those of appendicitis, or pain may occur regularly in the periumbilical area late after eating. Diarrhea, melena, or abrupt perforation may be the only manifestation. The condition is seldom recognized before operation is considered necessary for relief of acute abdominal emergency.

Medical Management. The rationale of the medical management of peptic ulcer is based on two adequately proved assumptions: (1) that gastric juice exerts a deleterious influence upon a defect of the mucosa of the stomach or duodenum, and (2) that the unusually powerful contractions, increased tone and spasm, which occur in the stomach or duodenum when empty, tend to inhibit healing. Since these phenomena produce notable discomforts, symptomatic relief and conditions favorable for healing of the lesion may be accomplished by a regimen which counteracts the erosive effect of the gastric secretions and at the same time quiets muscular activity.

The basic requirements of such a regimen are met by proper sedation and relaxation together with frequent administration of food and antacid substances. By keeping something in the stomach all the time, muscular activity is subdued and secretions are diluted, neutralized, or absorbed.

The aliment should be liquid, semisolid, or reduced to a pasty state, without coarse, rough elements. Hence, foods which may be finely divided, strained, puréed, or cooked to a soft consistency are chosen. Depending on the ingenuity of the physician and the cook and the financial status of the patient, a wide variety is possible. The basic foods of most ulcer diets are milk, butter, eggs, gelatin, custard, softened bread or toast, strained fruit juices, and sauces. To these are added cream soup, puréed vegetables, chopped or scraped meat or fish, mashed or baked potato, jelly, and similar substances (Table II).

The medicinal agents used in treating peptic ulcer are substances which neutralize the acidity of the gastric juice or by absorption inactivate the acid reaction. Most frequently

used have been sodium bicarbonate sodium citrate calcium carbonate calcium or magnesium phosphate bismuth subnitrate or subcarbonate and magnesium oxide Each has advantages and disadvantages

Sodium bicarbonate is soluble and likely to irritate the gastric mucosa and increase acid secretion although initially effective as a neutralizing agent Large amounts of sodium bicarbonate may disturb the acid base balance of the body especially in patients with pyloric obstruction or impaired renal or hepatic function If used continuously the total daily amount should be less than 4 gm *Magnesium oxide* has three times the neutralizing power of sodium bicarbonate and does not form gas but it is laxative and may cause a secondary rise of acid or acidosis *Calcium carbonate* has a low neutralizing value one-fifth that of sodium bicarbonate is insoluble not likely to disturb the acid base equilibrium and is not irritating but may induce constipation or flatulence The phosphate of calcium has similar properties and higher neutralizing capacity but may be irritating *Magnesium trisilicate* has been recommended as an effective antacid neutralization is apparently more prolonged than with other alkaline compounds and adsorbent and antiseptic activities are evident For these reasons magnesium trisilicate may be used as the last medication before sleep

Because of objections to the chemical substances mentioned other materials have been used Colloidal suspension of *aluminum hydroxide* is an effective antacid by adsorption and adsorption and is apparently nontoxic and does not disturb the acid base balance of the body When aluminum hydroxide is used with the usual ulcer diet magnesium in some form is required as a laxative Milk of magnesia may be combined with aluminum hydroxide gel Aluminum phosphate in suspension has been recommended instead of aluminum hydroxide particularly for the treatment of postoperative jejunal or stomal ulcers (Table II)

Suspensions of aluminum hydroxide have been combined with gastric mucin in a recently advocated preparation

A resin *amberlite IR IV* has been tried

with results as effective but no better than conventional substances

Protein hydrolysates have been recommended as aids to rapid healing of peptic ulcers The preparations are palatable taste badly and are inconvenient to administer Reported results do not show advantages over other forms of protein customarily used when malnutrition requires attention in the management of a particular patient Concentrated protein resident in the duodenum overstimulates gastric secretion

Enterogastrone extract of mucosa of hog's upper intestinal tract as now used is of no more value than conventional preparations for symptomatic relief and cure of peptic ulcer *Enterogastrone* administration is directed to prevention of recurrences but sufficient data have not been collected for definitive opinion of the efficacy of the product

An *antispasmodic* or a general sedative or both may be desirable *Belladonna* or *atropine* although of rather uncertain pharmacologic effect on gastric activity either motor or secretory is empirically satisfactory *Belladonna* may be combined with any of the powder preparations as the extract or given separately as atropine tablets or as tincture of belladonna by drops Synthetic antispasmodics are available As a general sedative small amounts of phenobarbital 15 or 30

p 339)

Acute Ulcer A patient with an acute ulcer should be in bed and the food intake restricted to fluids and semisolids frequently ingested in small amounts A modified Sippy regimen is simple practical and cheap (Table I) The hourly consumption of milk and cream is satisfactory and may be enriched if necessary by one of several protein carbohydrate concentrates reinforced with minerals and vitamins If the patient is obese or cream is not well tolerated skim milk may be used

If the onset of an ulcer or an exacerbation is fulminant with severe pain and vomiting sedatives or opiates may be required before oral feeding is tolerated Effervescent bromide mixtures may suffice but if not retained hypodermic or intravenous barbitu

rates may be necessary. Opium derivatives should be withheld until other resources fail, and when mandatory, administered hypodermically in adequate amounts. Demerol, 100 mg. with codeine sulfate 0.06 gm., should be tried, morphine sulfate in 15, 20, and 30 mg. doses, with or without atropine as indicated, ■ often the eventual recourse. Rarely

fusion

Perforation Perforation of acute or chronic ulcer demands surgical treatment as soon as recognized. For a few cases, if rupture occurred when the stomach was empty, if air is not demonstrable under the diaphragms, and if peritonitis is not evident, conservative management by intragastric suction and supportive measures may be permissible.

Hemorrhage After massive hematemesis or melena, and until the status of the patient ■ determined, absolute physical immobility and mental calm should be assured by 15 mg. of morphine sulfate, parenterally administered. Grouping and typing of blood should be done immediately, and suitable donors chosen. Bleeding into the upper intestinal tract of 90 cc. for a relatively short period will produce a recognizably black stool. Rapid loss of 1000 cc. or more of blood may cause diarrhea with notably red feces. Prompt transfusion of whole blood will prevent dilution of circulating blood and dehydration, provide elements essential for clotting, and partially supply nutriment. If blood ■ not available, plasma, protein mixtures

safely by a skillful and experienced endoscopist to find a bleeding point in the stomach, or to note reflux of blood from the duodenum through the pylorus.

Estimates of hemoglobin and counts of red blood cells are not dependable indices of the extent or duration of hemorrhage. Dilution by accessions of tissue fluid or from solutions introduced parenterally, or effects of transfusions of blood, will alter the absolute and relative amounts of the several constituents of the circulating blood. Chemical analysis of the stool for blood yields no enlightening information of the amount of blood lost or termination of the hemorrhage; occult blood may be detected in the feces for days after bleeding has stopped.

Blood pressure registers more accurately than hemoglobin estimation the amount and progress of bleeding; circulatory tension should be determined every hour until a stable level is maintained. Supportive transfusions of whole blood or other material should be started promptly when systolic pressure is 90 or below. All intravenous infusions should be given slowly, as continuous drip, at the rate at which the number of drops per minute sustains peripheral vascular pressure and does not rapidly increase the volume of circulating blood.

Oral feeding ■ begun as soon as the patient is quiet and shock condition has been corrected, according to the schedule outlined for acute ulcer (Table I). Gelatin or glucose or both may be added to the milk and cream with advantage, the gelatin may contribute to coagulation. The formulas used by Andersen are

Glucose	60 gm
Cream, 20 per cent	120 cc
Milk	880 cc
or.	
Gelatin	30 gm
Glucose	60 gm
Cream, 20 per cent	100 cc
Milk	900 cc

These mixtures are kept cool, the one with gelatin not refrigerated, and fed cool or warm in quantities prescribed.

Continuous instillation of either of these mixtures, or of milk with aluminum hydroxide, citrated milk, or protein solutions, through indwelling gastric or duodenal tubes, has been advocated for immediate

hours, surgical intervention should be seriously considered, and if operation ■ done, a competent surgeon and all equipment, personnel, and adjuncts should be available for gastric resection. Unless the exact site of the hemorrhage is known from previous examination, time lost in searching for the bleeding source may be fatal. A fibrotic or sclerotic vessel in an old callous scar does not readily retract or close, and is not easily securely tied.

Gastroscopic examination may be done

alimentation after hemorrhage from the stomach or duodenum, but such performance is no more efficacious than frequent oral feeding, and is uncomfortable for the patient and consequently prevents the requisite repose and relaxation.

Stools should be kept soft and defecation made easy by mild laxatives, oil, or low rectal enemas. Straining to evacuate a hard fecal mass may incite bleeding from a partially or completely clotted source.

Meulengracht has since 1931 recommended free feeding for a bleeding peptic ulcer. From the first day patients are fed a full pureed diet, including tea, white bread and butter as breakfast, oatmeal porridge with milk, white bread and butter at 9 A.M., dinner at 1 P.M., milk or cocoa at 3 P.M., and egg, sandwiches of sliced meat or cheese, and tea at 6 P.M. The dinner comprises different kinds of gruel, porridge, vegetable soups, meat balls, timbales, chops, omelet, fish balls, vegetables au gratin, meat au gratin, fish au gratin, mashed potato, vegetable purées, creamed vegetables, stewed apricots, apple sauce, rice and tapioca puddings. Water and milk are served according to the patients' desires.

The objective of any method is to replace blood loss, quantitatively and qualitatively, as effectively as possible. And to this end, periods of enforced starvation while waiting cessation of hemorrhage, and in fear of aggravation of bleeding, have been abrogated in favor of activities directed to rapid and complete restoration of blood constituents and volume. When ambulant feeding is begun, ferrous sulfate, 10 to 15 gm. daily, may be given.

Roentgen examination to locate the source of bleeding should be deferred until after the hemorrhage has ceased so that dislodging a clot by the heavy barium suspension and manipulation is improbable. When painless

Obstruction and Retention The stomach may not empty properly because of cicatricial stenosis of the duodenum, obstruction by inflammatory edema often with coincident spasm, or from interference with gastric motor function by a saddle ulcer on the lesser curvature. In any cases of obstruction or retention the management is basically that of an acute ulcer. That is, the patient should be in a hospital, in bed, and the stomach should be completely emptied by tubal aspiration and lavage. The large Ewald tube with suction bulb is probably the simplest apparatus for initial evacuation of the stomach. Thereafter feedings as prescribed for acute ulcer are instituted (Table I).

Stomach contents are thoroughly removed 3 hours after the last feeding each day and the amount recovered is measured and recorded. If the quantity of gastric residue progressively diminishes, and the patient is quiet and comfortable, the program may be continued as designed for acute ulcer, under the assumption that the inflammation and spasm are subsiding. If, after 5 to 7 days, the stomach retains as much or more than before treatment began, organic, mechanical, permanent obstruction may be presumed and operative intervention considered necessary. Adjunctive measures may be required for sedation and local relaxation. Combinations of phenobarbital and belladonna or atropine are as satisfactory as any of the synthetic preparations.

An indwelling intranasal tube may be introduced into the stomach or duodenum through which feeding mixtures and antacids are instilled. The flow of nutrient or solution is stopped periodically and, after a suitable interval, suction applied. The quantity of stomach residue aspirated determines the amount of subsequent feedings, and the permanence or recession of the obstruction. However, the objections made to intubation for treatment of hemorrhage or acute ulcer apply to instances of obstruction. The intranasal tube is an annoyance and the discomfort annuls the theoretical benefits.

When the course of events with uncomplicated acute ulcer, with bleeding ulcer, or with obstruction or retention is favorable, medical management may proceed through 3 weeks, and an ambulant program begun the 22nd day (Table II).

of inflammatory edema. When the existence and site of an ulcer are known investigation may be delayed. When reasons prevail to bring into consideration cancer of the stomach as the origin of hematemesis or melena prompt roentgen or gastroscopic examination may be advisable.

Ambulant Management. An ambulatory regimen is applicable for most of the patients with simple, uncomplicated, benign peptic ulcer. Instructions should be specific and preferably printed in some form that may be given to patients. The purposes and objectives of the diet and medication should be explained in plain terms. After trial of the standard program for 10 to 14 days, the patient should report results, residual symptoms, and discuss articles of food habitually eaten but not mentioned in the list issued. Adjustments for the individual are made at this time and the modified schedule is continued for 8 weeks.

After approximately 8 weeks from start of treatment, radiologic observation of results is made. At this time a simple ulcer has healed and medication is gradually stopped, No 1 first, then No 3, and finally No 2. If discomfort is felt when No 3 is eliminated the accustomed dose should be resumed. Sufficient amounts of No 2 should be taken as necessary for regulation of bowel function. Usually the antacids and correctives are readily suspended and a protective diet of three equal meals with glasses of milk between suffices for several months. If a sedative antispasmodic prescription has been necessary, this should be continued. Vegetable need not be puréed if amenable to softening by cooking, but should not be served raw. Fruits with skins and seeds should be cooked and strained. Meat should be grilled, broiled, or roasted, not fried, stewed, or boiled.

The patient is advised to revert to a strict ulcer regimen during colds, any acute febrile disease, or when unavoidably subjected to continuous fatigue, mental strain, or emotional disturbance. At this point the physician should be well acquainted with the patient's personality, environment, and reactions to problems and conflicts, and be prepared to plan and advise conduct that may prevent exacerbation of the ulcer or recurrent consequences.

Treatment of peptic ulcer must be treatment of the individual. Many factors influence unfavorably the fate of a particular patient. Fatigue and exposure, infections, anxiety, grief, emotional shock, and inability to eat proper food at regular intervals may

impair or destroy tranquility, solution of an emotional or financial problem, elimination of sources of repeated infectious insults, protection against excessive fatigue may be more important than details of medical management or technic of surgical treatment. An environmental conflict may compel an individual to behave against his natural inclinations with consequent resentment, psychic turmoil deranges secretory, circulatory, and motor controls in general and, in some, of the gastro intestinal tract in particular. This consideration is the basis for explaining peptic ulcer in terms of somatic manifestations of psychoneurosis. Peptic ulcer is not fundamentally a psychosomatic disease, but

complete, successful treatment of a particular patient.

Medical treatment often fails because the patient cannot or will not co operate. Medical programs carelessly planned and indifferently supervised are doomed to failure. An ulcer may be apparently refractive because the host is recalcitrant or because the directing physician is ignorant or incompetent. Under these circumstances the assumption of intractability of the ulcer is not valid and resorting to surgery will not be justified.

Surgical Treatment. Surgery demands consideration in medical therapy of peptic ulcer, not in respect of technic, but of policy. That is, sound medical judgment should determine when and under what circumstances surgical intervention should be made in a particular instance. The decision concerns the summary of the course and the momentary status of the individual ulcer.

Perforation as the first event, or consequent penetration of a chronic gastric or duodenal ulcer, requires surgical treatment, methodically qualified as discussed. After perforation of a duodenal ulcer, symptoms recur in 60 to 65 per cent of cases, with gastric ulcer, sequelae appear after seven or eight perforations. A penetrating ulcer with the base of a crater adherent to, or actually

formed by tissue of an adjacent organ usually the pancreas or liver will not heal and requires surgery. Proved mechanical duodenal obstruction by a stenotic cicatrice obviously must be surgically relieved. For old people simple gastro enterostomy is satisfactory. Hourglass contracture of the stomach caused by the chronic fibrotic ulcer can be corrected only by surgical means.

For continuous bleeding after 48 hours in patients over 45 years of age surgical exploration is probably advisable. But in this event facilities and preparations for gastroduodenal resection must be assured. Search for source of bleeding contemplating ligation of a vessel is futile.

The value of a surgical procedure for non obstructive benign recurrent duodenal ulcer which has not bled is debatable. Simple gastrojejunostomy has been abandoned except for special cases. A satisfactory operation for peptic ulcer is resection of 75 per cent of the distal part of the stomach and the first part of the duodenum according to the Hofmeister or Billroth II technic with a short loop reverse jejunostomy. When a duodenal ulcer is irremovably fixed to adjacent organs the pyloric antrum in such case should be excised with three fourths of the body of the stomach.

Vagotomy or section of all branches of the vagus nerve accessible below the diaphragm with or without gastro enterostomy is currently advocated for chronic duodenal ulcer of young or middle aged adults. Even though the result is not below from data

motility has been an unfortunate consequence of many vagotomies. Addition of vagotomy to the operation of subtotal gastrectomy is of slight value and that only to prevent possible recurrences. Most of the

combined with gastrojejunostomy is not advisable for ulcer of the stomach in any event. A gastric ulcer which does not heal with competent medical treatment is probably malignant and requires extirpation by partial gastroduodenal resection.

Subdiaphragmatic section of the vagus nerve is applicable in instances of recurrent ulceration or hemorrhage after gastro enterostomy or partial gastric resection.

Gastrocolic fistula as a consequence of penetrating postoperative jejunal ulcer is a surgical problem.

Gastritis—superficial catarrhal hypertrophic and atrophic—is seen through the gastroscope in stomachs after gastrojejunostomies or in gastric pouches after partial or subtotal resections. When the diet is properly regulated this form of mixed gastritis is seldom conducive of symptoms.

Other unfortunate sequelae of gastric resection are due to rapid emptying through the artificial stoma. Caused either by direct stimulation of excessive insulin secretion from the presence of abundant food substance in the jejunum or by more complex mechanisms initiated by intestinal distention, physical sensations attributable to hyperglycemia and splanchnic vascular disturbance frequently occur soon after meals. Also the glyc

the after eating. Either of these syndromes or both may occur in one patient and may be corrected by frequent feedings of small quantities of food preferably protein in composition.

Ulcer is such a common ailment afflicting so many people and causing so much disability that any physician attempting to treat it should carefully study the whole ulcer problem and the individual concerned in order to apply the best judgment in management. No other disease demands such close doctor patient relationship.

An editorial in the *British Medical Journal* states that the medical profession has learned too slowly that neither the dramatic intervention of surgery nor the elaborate ritual of the alkaline diet can banish the constitutional tendency to peptic ulceration. To separate the ulcer patient from his diathesis is like severing the fisherman from his soul, and until some new secret of nature is revealed the patient must be taught how best to live at peace with his ulcer. And to do this he must learn how to live at peace with himself.

TABLE I

BASIC MANAGEMENT FOR ACUTE PEPTIC
ULCER

(This Program May Be Administered at Home with Competent Attendants)

First week Three ounces of $\frac{1}{2}$ milk and $\frac{1}{2}$ cream every hour 7 A.M. to 9 P.M. If cream is not well tolerated whole milk 3 oz (90 cc) each feeding or skimmed milk with a powdered compound of protein and carbohydrate added 1 part of powder to 11 or 8 parts of milk by volume may be used. Most of these preparations contain minerals and vitamins. Dietene or Meritine are examples.

Second week Eighth day add one egg poached or soft boiled to 12 o'clock feeding and a small saucer of cooked cereal (cream of wheat farina) at 8 A.M. and 6 P.M.

10th day add one piece buttered toast to 10 A.M. and 4 P.M. feedings and a soft boiled or poached egg at 2 P.M.

12th day add one soft boiled or poached egg to 8 P.M. feeding and gelatin (jello) at 9 A.M. and 1 P.M.

T¹

P.M. and plain icecream at 7 P.M.

11 30 A.M. 1 P.M. 2 30 P.M. 4 P.M. 7 P.M. 9 P.M. and add at 7 A.M. egg and toast at 8 30 A.M. cereal at 10 A.M. milk jello with cream and plain sugar cookie at 11 30 A.M. cream soup and soda crackers at 1 P.M. egg and toast at 2 30 P.M. rice or tapioca custard and plain cookie at 4 P.M. icecream and plain cookie at 5 30 P.M. pureed vegetable $\frac{1}{2}$ egg and toast at 7 P.M. potato with butter at 9 P.M. cooked strained fruit sauce and plain cookie

If pain occurs between feedings 1 or 2 teaspoonfuls of suspension of aluminum hy-

drate magnesium oxide or milk of magnesia may be prescribed in appropriate amounts

TABLE II

AMBULATORY SCHEDULE

7 A.M. 1 tablespoonful No 1* in half a glass of water

7 30 A.M. Strained fruit juice or fruit sauce baked apple without skin seeds or core Soft boiled egg with one slice buttered toast or poached egg on toast Cooked cereal (cream of wheat or farina) with cream and sugar

Glass whole milk heated or cool
8 30 A.M. Half a teaspoonful No 2** with $\frac{1}{2}$ glass of water

10 A.M. Glass whole milk or milk with protein carbohydrate powder added

11 A.M. Two teaspoonfuls No 3*** in a glass of water

12 30 P.M. Cream soup
White bread or rolls buttered
Vegetable pureed strained or mashed $\frac{1}{2}$
Baked or mashed potato $\frac{1}{2}$ boiled rice

* No 1 is kaolin and aluminum hydroxide (Kao-mag)

** No 2 is a powder composed of calcium carbonate calcium phosphate and heavy calcined magnesia (magnesium oxide) in proportions adjusted to individual requirements of bowel function

*** No 3 is aluminum hydroxide (amphojel) or aluminum phosphate (phosphajel) or mixture of aluminum hydroxide and magnesium trisilicate preparations may be taken in tablet form if liquids

radical change in usual diet If the laxative is not

$\frac{1}{2}$ Vegetables with shells (beans corn) or seeds (tomato) should be well cooked and strained those with husk (peas) may be pureed others with skin or stalks that may be removed (carrots cauliflower asparagus) may be well boiled and mashed

For package lunches sandwiches may be made of bread and butter with cream cheese jelly

few punches of cocoa powder

macaroni, spaghetti, or noodles, with butter or vegetable juice

Custard pudding, with rice, tapioca or bread, jello with cream and sugar

Cooked, strained fruit sauce or plain ice-cream

White cake, angel food, sponge cake, or sugar cookies

Glass whole milk

1 30 P.M. Half a teaspoonful No 2 ** with $\frac{1}{2}$ glass of water

3 P.M. Same as at 10 A.M.

4 30 P.M. Two teaspoonfuls No 3 *** in $\frac{1}{2}$ glass of water

6 P.M. Same as 12 30 P.M. with addition of broiled or roasted beef, mutton, lamb, fish, chicken, turkey, squab, guinea hen, calf liver, sweetbread, or oyster

7 30 P.M. Half a teaspoonful No 2 ** with $\frac{1}{2}$ glass of water

9 P.M. Two teaspoonfuls No 3 *** in $\frac{1}{2}$ glass of water

At bedtime glass of milk with bread and butter, and jelly or cream cheese sandwich, cottage cheese, plain sugar cookie or graham cracker, or fortified milk, or half a glass of water with 2 teaspoonfuls of No 3

necessary, No 1 or No 3 should be substituted at hours designated for No 2, that is, something must be taken as scheduled

These diets may require modification for patients with heart or kidney disease, diabetes mellitus or obesity. Actually, association of peptic ulcer with other systemic disease, particularly diabetes is rare.

JAMES B. CAREY

During the past few months, following completion of the preceding discussion of peptic ulcer, there has been renewed interest in the use of autonomic blocking agents in the treatment of ulcer. In an effort to diminish gastric secretion and to decrease motility of the gastro intestinal tract several cholinergic blocking agents have been tried with little success. However the development of methantheline bromide (B diethylaminoethylxanthene 9-carboxylate methobromide), marketed under the trade name of Banthine may prove to be the type of drug long sought in ulcer management. It is too early for accurate evaluation but several observers* have indicated that this preparation is a valuable addition to drug therapy of peptic ulcer.

The drug is usually prescribed in 50 to 100 mg doses every 4 hours day and night during the acute stage. After healing is well in progress the dosage may be lowered, but administration of the drug every 6 hours must continue indefinitely.

It must be emphasized that this drug is only an adjunct to the usual measures of diet rest and relaxation and its true usefulness will need more time for accurate evaluation.—Editor

* Grunson, K. S. A Clinical Trial of Banthine in Cases of Peptic Ulcer. *Gastroenterology* (In Press)

Gonginis, F. H., et al. An Orally Effective Quaternary Amine, Banthine Capable of Reducing Gastric Motility and Secretions. *Gastroenterology*, 14: 301, 1950

DISEASES OF THE SMALL BOWEL AND COLON

REGIONAL ENTERITIS

A subacute or chronic destructive, exudative, and proliferative regional inflammatory process has been observed in the small intestine from time to time by clinicians, roentgenologists, and surgeons. This condition was well described by the late Dr. William J. Mayo as long ago as 1893. For many years it was thought that the lesion was limited to the distal part of the ileum and even in the rather accurate description of the condition by Crohn, Ginzburg, and Oppenheimer in 1932, the impression is given that the lesion is limited to the distal part of the ileum or to the bowel contiguous to the distal part of the ileum, or to both. However, a similar pathologic process has been found to involve, although somewhat less frequently,

all segments of the small intestine, and to be localized high in the jejunum as well as in the distal part of the ileum.

Treatment. For the present, treatment varies for the localized granulomatous form of regional enteritis, the extensive ulcerative form, and the recurrent lesions.

The treatment of the granulomatous enteritis in its localized form is largely surgical. Ileocolostomy and subsequent resection of the diseased segment of the bowel are the treatment of choice. However, when to operate and how extensively to resect are questions that only experience and long follow up can answer. It is definitely not wise to operate during the acute or subacute phase of the disease. It is here that the medical treatment becomes particularly important. Adequate rest, a low residue diet, and the administra-

tion of one of the sulfonamides should be continued until the patient is free of fever, the tenderness in the abdomen has largely subsided, and the acute infectious phase has been overcome.

So far the sulfonamide drugs of choice for use in these cases have been succinylsulfathiazole (sulfasuxidine) and phthalylsulfathiazole (sulfathaladine). Administration of 12 gm of sulfasuxidine, in divided doses of 30 grains (2 gm) every 4 hours or of 120 grains (8 gm) of sulfathaladine in a similar manner has often been followed by a prompt subsidence of the acute and active symptoms. If the condition is of the localized granulomatous process, then surgical intervention should be carried out as soon as the acute symptoms subside and the patient's condition warrants.

What has been said about the medical treatment for the localized disease should be adhered to more generally and for longer periods in cases in which the disease is of the ulcerative type. For such cases it may be wise to continue the medical management for weeks or months as follows: the sulfonamide drugs should be taken for a period of 2 weeks, then the patient should have a week of rest, and then treatment with the drugs should begin again. Streptomycin has been helpful in some of these cases. It can be given in divided doses averaging a total of 2 gm a day. There is some evidence that the combination of streptomycin and sulfathaladine each in smaller amounts than those mentioned has greater value than either one alone. When the condition has become quiescent and there is no evidence of spreading, surgical intervention may be advisable in a fair number of these cases.

Recurrence of the localized granulomatous type of the disease after resection is rare, but recurrence of the extensive ulcerative type is common. This fact makes it necessary to consider the third part of the program of therapy. Roentgen therapy has been used for recurrent regional ileitis for a number of years. Early impressions indicate that it is a reasonable and satisfactory palliative procedure. Although the technical procedure of treatment is not too well established, it seems advisable to expose the entire abdomen to roentgen rays at a moderate voltage. The dosage is the same as that commonly used

in treatment of chronic inflammatory conditions.

Treatment with roentgen rays has produced striking results in selected cases. It was first applied in treatment of recurrent lesions when resection did not seem advisable. As experience grew it was used in earlier cases and particularly in cases of the ulcerative form.

If the disease recurs even though the recurrent involvement may not be especially extensive, there seems to be some secondary effect on intestinal absorption so that eventually in p
least 140 gm or more of protein a day. It should be low in residue. In addition, in cases of recurrence in which steatorrhea is present, the diet should be low in fat, similar to the diet for sprue. Striking changes for the better have frequently been noted when fat is eliminated from the diet and the patient is given a diet high in protein. Excessive amounts of vitamin B complex as well as generous amounts of other vitamins, particularly vitamins A, C, and K, have been helpful in keeping these patients in good condition. Doses of 100,000 international units of vitamin A, 200 mg of vitamin C, and 4 to 8 mg of vitamin K should be given daily. Various preparations of amino acids given by mouth in large amounts have been particularly helpful in giving these patients adequate amounts of protein. It is essential that a preparation be chosen which contains all the essential amino acids. Unless this is done their administration will be useless.

Prognosis. The prognosis for patients who have granulomatous ileitis is good after resection for, in general, less than 5 per cent have recurrences. However, among patients who have the ulcerative form of the disease the rate of recurrence is high and is probably nearly 20 per cent, or even more. For patients who have ulcerative lesions then, all reasonable measures of treatment must be invoked. It is of particular interest to note that such patients may have had a resection and may have remained well for 10 to 12

as during the recent war, recurrence may

take place. It is obvious that these recurrences are not due to the fact that enough tissue is not resected. There must be some smoldering infection in the lymph nodes of these individuals or a latent infection somewhere in the abdomen which remains under control for some time and then when resistance is lowered, it flares up again. This all points to the fact that perhaps if the cause of the disease were known its final treatment would be better understood.

J. ARNOLD BARGEN

REFERENCES

- Crohn B B, Ginzburg L and Oppenheimer G D: Regional Ileitis Pathologic and Clinical Entity *JAMA* 99 1323 1932
 Mayo W J: Quoted by Borgen, J A: Regional Enteritis Relation of Its Onset Clinical Course and Pathologic Manifestations to Its Cause *Wisconsin M J*, 38 877, 1939

ALIMENTARY TUBERCULOSIS

Tuberculosis is probably the oldest known cause of dysentery. Tuberculous colitis is part of the intestinal involvement that occurs secondary to tuberculous disease of the lungs or other bodily structures. It is a serious complication. In most cases the primary tuberculous lesion is situated in the lungs.

The disease can be divided into two clinical types: (1) the ulcerative type and (2) the hyperplastic type. The former usually occurs in the course of active pulmonary disease. The latter may occur as a late sequel of an otherwise quiescent pulmonary lesion and may even occur without the presence of the pulmonary tuberculosis being proved.

Management. Since the two forms of this disease as they affect the intestine are different pathologically, the program of management also will be different. By and large, it can be said that tuberculosis is essentially a medical disease regardless of the site of the lesion, however surgical measures are used as an adjunct to careful medical supervision. There is no specific treatment for ulcerative intestinal tuberculosis.

Since the success of treatment is largely dependent on the stage of the disease at which the diagnosis is made, the importance of early diagnosis cannot be stressed too

strongly. As soon as the presence of an intestinal lesion is suspected, the chief objective of treatment should be to take as much of the burden as possible off the inflamed and handicapped bowel.

A smooth diet of rather low residue is indicated. It may be wise to suspend the forcing of food. It is probably a good plan to use this type of treatment in any case in which the presence of an intestinal lesion is suspected. Roughage should be eliminated from the diet as far as possible. Fresh fruit juices and purées should replace the more fibrous raw fruits, vegetables, and salads. Raw milk

The diet outlined for patients who have chronic ulcerative colitis will be applicable in most cases of intestinal tuberculosis.

Phthisiologists frequently have mentioned the importance of adequate vitamins in the diet as well as the value of increased amounts of protein foods. Extra amounts of cod liver oil, citrus fruits, and, particularly, tomato juice have been advocated and their use has resulted in a marked reduction of intestinal symptoms and a great gain of weight. When constipation is disturbing, some soft bulk may be added.

Colonic irrigations with physiologic solution of sodium chloride and so-called intestinal antiseptics have been used and seem to be worth while for their cleansing qualities when diarrhea is severe. If given as warm enemas, at bedtime, they may afford the patient more rest and sleep.

Rest, as in all forms of tuberculosis, is the keystone of treatment. The patient should be in bed until he is afebrile and until symptoms of dyspepsia have disappeared, then carefully graded activity is in order.

Injection of oxygen into the peritoneal cavity has been advised and in selected cases has produced good results. Roentgen therapy also has proved beneficial in some cases.

Heliotherapy, cautiously applied over parts of the body and finally over the whole body, is useful. This type of therapy is generally accepted by all who have had extensive experience in treating this condition. Ultraviolet light seems to have value and in the hands of some workers the effects of this

type of therapy have been found superior to those of sunlight

Many drugs such as compounds of arsenic calcium and mercury have been used. Thus acetarsone (acetyl amino hydroxyphenyl arsonic acid) and treparsol (formyl amide of meta aminopara oxyphenylarsonic acid) have their advocates. Calcium gluconate and a solution of parathyroid and calcium chloride have been injected intravenously over long periods. For the active diarrhea the ordinary drugs recommended in the chapter on thrombo ulcerative colitis are indicated.

As with other forms of ulcerative colitis some of the drugs of the sulfonamide series have received experimental and clinical trial. Of the drugs that have been administered to modify inhibit or prevent tuberculosis in guinea pigs sulfanilamide sulfapyridine azosulfamide promin (sodium p p diamino diphenylsulfone N N didextrose sulfonate) and some other drugs which have been introduced more recently have produced satisfactory results. The dosage of these drugs must be individualized for each patient.

Many drugs have been given in the hope that they might have a specific effect on the tuberculous process. Some years ago promin gave hope because of its favorable modification of the course of tuberculosis experimentally produced in guinea pigs. However later studies did not justify the earlier hopes. With the advent of the antibiotics these were tried successively. It has been shown that streptomycin or dihydrostreptomycin 2

in pulmonary and renal disease but favorable results also have been obtained in some cases of intestinal tuberculosis. Finally as in pulmonary tuberculosis care in a sanatorium is definitely indicated in cases of ulcerative tuberculosis of the intestine. There is con

which the ileum was completely transected and then transplanted into the colon below the diseased segment. The involved segment is not removed surgically nor is its removal advocated. Observation of patients for a number of years after they have been treated in this manner has indicated that this type of treatment may be of value.

In the case of the hyperplastic form of tuberculosis when this lesion involves a local segment of bowel as it usually does intestinal resection or at least diversion of the fecal stream by ileocolostomy or colocolostomy is the treatment of choice. This type of tuberculosis often causes obstruction partial or severe and by interfering with digestion impedes healing of a smouldering pulmonary lesion. When obstruction is relieved by a short circuiting operation the lung will be given greater opportunity to heal. In some cases after this type of surgical treatment the lesion in the segment of the bowel which no longer functions will tend to dry up and heal. However secondary resection usually will be indicated.

ILLUSTRATIVE CASE. A married woman aged 48 years came to the Mayo Clinic on Sept. 29, 1941, because of pain in the right lower abdominal quadrant, episodes of intestinal obstruction, weakness and loss of weight of a year's duration. Although these symptoms had been present for that length of time they had been much worse in the 6 months before the patient came to the clinic. In April, 1941, she had suffered from severe pain in the abdomen and nausea and vomiting. These symptoms had lasted for 6 days and during that time she had not had any bowel movement and had not passed any gas. She had had several similar attacks in the subsequent months with periods of loose stools between the attacks.

On admission she weighed 94 lbs (42.6 kg) whereas her normal weight the year before had been 120 lbs (54.4 kg). Her temperature was 98° F. Numerous stools were examined. No unusual parasites, ova, bacteria or acid fast organisms were found. The sedimentation rate

normal. The sedimentation rate of the erythrocytes was 48 mm in one hour. The values for the total acid and the free hydrochloric acid in the gastric contents were 56 and 38 respectively when determined by the method of Topfer. Roentgenologic examination with a bar

gators have advised operation in the ulcerative form of tuberculosis if and when the pulmonary condition is satisfactory or quiescent. Argentine investigators particularly favor this course and during a recent visit to Buenos Aires the writer saw the results of such treatment and observed an operation in

ium enema revealed a long tumefactive lesion which involved the cecum ascending colon and the terminal portion of the ileum. This did not have the appearance of any specific inflammatory process. There was no unusual hypermucosality of this segment of the bowel. It was felt that the lesion might be a tuberculoma or a mebic granuloma. The administration of 4 grains (0.26 gm) of emetine hydrochloride in divided doses and 46 grains (3 gm) of trepar sol during a period of 4 days did not have any effect on the symptoms or on the roentgenologic appearance of the lesion. The tenderness in the right lower quadrant of the abdomen persisted. Ileocolostomy was performed for what was described as a large inflammatory granuloma. Two lymph nodes from the adjacent mesentery were

the cecum and ascending colon was performed for ulcerating and hyperplastic tuberculosis of these portions of the intestine. The patient made an uneventful recovery.

This case illustrates that tuberculosis can exist in the intestine as a primary process without evidence of tuberculosis elsewhere in the body.

Treatment of Complications For some of the complications surgical intervention occasionally will be indicated. When such is the case, treatment will have to be individualized and the complication considered as a disease apart from the basic lesion.

J. ARNOLD BARGEN

REFERENCE

Bargen, J. A. *Modern Management of Colitis*. Springfield, Ill.: C. C. Thomas, 1943.

CHRONIC THROMBO-ULCERATIVE (STREPTOCOCCAL) COLITIS

Since uncertainty regarding the cause of some forms of ulcerative colitis still exists, it seems particularly important to set forth clearly the nature of the ulcerative colitis under consideration when therapy is being considered.

In this article we shall consider that form of ulcerative colitis which has its inception in the most distal portion of the wall of the rectum and spreads relentlessly orad from that point. This disease involves the wall of the bowel, the mucous membrane is involved

only secondarily. Involvement is diffuse. The disease begins in the submucosal structures as a thrombotic process and produces a granular, easily bleeding, edematous mucous membrane, diffuse narrowing of the intes-

defined group of symptoms, varying with the progression of the disease and the interjection of various complications and sequelae which may be associated with or follow the progressive, destructive process. Rectal bleeding is a pathognomonic sign. The amount and severity of the bleeding will vary with the extent of involvement and with the rapidity of its progression. If the involvement is extensive, diarrhea and dysentery will be severe. When an attack occurs in a fulminating manner, the patient may be overwhelmed by a combination of these symptoms and signs. This condition has been commonly designated as "thrombo-ulcerative colitis," or as "streptococcal ulcerative colitis."

The large majority of patients suffering

tion between internist and surgeon is so valuable as it is among patients afflicted with this malady. In the last decade, the attitude of physicians toward the disease has changed from one of hopelessness and despair to one of hopefulness and accomplishment.

It is well to think of this disease as the modern practitioner thinks of tuberculosis. One should not speak of its cure but of its control.

This is a disease in which wise guidance of the patient by the general practitioner for a long period is essential. Treatment should be based on the following convictions: (1) that the condition is an infectious disease of the large intestine, (2) that uncomplicated thrombo-ulcerative colitis is a medical problem, and (3) that certain complications are definite indications for operation.

Medical Treatment In cases of thrombo-ulcerative colitis in which such complications as neoplasm, polyposis, stricture, perirectal abscess, perforation, or nephrolithiasis do not exist, the disease is a medical problem.

Moreover most of the other complications described fall in the realm of the internist

REST AND RESTFUL RECREATION—In acute fulminating thrombo ulcerative colitis rest in bed and absolute quiet should be maintained until the patient is free of fever and then there should be a gradual return to physical activity To rest the intestinal tract it may be necessary to withhold food by mouth and to give fluids parenterally In the more chronic but severe type of the disease without fever restful recreation is important By this is meant that the patient should not be kept in bed but should follow a positive program of mild activity Reading short walks and mental diversion are helpful Patients who have the disease become discouraged easily The slightest change of symptoms which is not for the better may undo days of improvement because of the patient's mental attitude toward such a change Patience and perseverance on the part of the physician and an optimistic viewpoint are essential Occupational therapy in many forms can be made interesting This type of diversion is invaluable for it tends to distract the attention of the patient from his need of remaining near a toilet room

DIET The feeding of patients who have this disease is one of the most difficult dietary problems in medicine It seems that in the past many physicians have too greatly restricted the amount of food allowed these patients and as a result the patients have lost strength and their ability to fight the infection In the active stage of the disease there is invariably a lagging of appetite or complete anorexia The problem then is first one of creating an appetite and next one of giving foods which are digested almost entirely in the stomach and small intestine and which thus leave little residue in the colon The foods prescribed should vary with the stage severity and complications of the disease When the symptoms are acute the patient may be able to take only a small amount of highly concentrated food In cases in which the disease is more severe it may be necessary for a time to give nothing but liquids by mouth In the cases in which the disease is particularly severe a solution of 5 or 10 per cent dextrose can be injected intravenously and large amounts of physio

logic solution of sodium chloride can be injected under the skin

In the average case however the essential features to be considered in the diet are that it shall not be irritating that it shall be of low residue that it shall have an adequate content of calories proteins vitamins and minerals and that it shall be offered as attractively as possible Some of the foods of low residue are lean meats rice white bread Italian pastes sugar well cooked and strained cereals cooked eggs butter and cream Proteins in most forms are desirable Vitamins can be supplied in concentrated form in fruit juices yeast butter wheat germ cod liver oil or irradiated ergosterol Contrary to the usual assumption milk is not a low residue food and it is not well

■ milk
often
these

patients in the hospital where their activities can be controlled accurately even though they may not be acutely ill On this basis a definite dietary program has been outlined On admission the patient is given strictly bland food to which additions are made at regular intervals One may start at various stages of this program but few patients will tolerate the full diet from the beginning

Additions to the foundation diet will result in a full diet containing 140 gm of protein and 3400 calories Jelly or jams without seeds may be served if desired Beverages should not be iced but rather should be lukewarm Icecream should be eaten slowly Condiments such as mustard horse radish catsup vinegar and highly seasoned sauces or relishes are best avoided

Although the diet is thus based on broad general principles it must still be made individual for as with many other conditions few patients react similarly to any given program It must be graded up or down to fit individual needs Occasionally in the late stages of the disease peripheral neuritis has been noted and patients so afflicted will respond dramatically to the administration of large amounts of thiamine chloride In a few cases marked reduction of dark adaptation has been noted This can be relieved by the administration of large amounts of vitamin A At times as much as 100 000 international units has been given daily A

there will be marked reduction of the ascorbic acid content of the blood serum because the patients have been afraid to take adequate quantities of citrus fruits. Such patients are aided materially by being given extra amounts (200 to 300 mg daily) of synthetic vitamin C in tablet form. Finally, there is the rare patient who has one or several massive hemorrhages because of a reduction of the concentration of prothrombin in his blood. Such a patient receives dramatic relief by being given vitamin K, either by mouth or by vein. Klotogen (vitamin K concentrate in peanut oil) or menadiolone (2-methyl-1,4-naphthoquinone) may be administered. Klotogen may be obtained in capsules, each of which contains 1000 units of vitamin concentrate. From 6 to 9 of these capsules may be administered daily. Menadiolone bisulfite may be administered intravenously in doses of 1 gram (0.065 gm).

Except in these unusual situations, vitamin concentrates are used only to assure that the diet will not be lacking in any of these

hospital staff or by helpful persons in the patient's home. Freedom from worry and emotional strain is important. Fatigue and nervous excitability interfere with a patient's progress. It is important to keep the patient warm and to maintain the fluid balance. Occasionally, hot abdominal stupes seem to give much comfort. The great urgency of movement of the bowels and the straining at the stool must be allayed. This can be done by judicious psychotherapy. Sufficient sleep is most helpful. The many little comforts which are accorded patients who have any serious illness cannot be overemphasized in these cases.

DRUGS Tincture of opium may be given in minimal amounts. The deodorized tincture can be given in doses of 5 to 10 minims (0.3 to 0.6 cc) three or four times a day. It is best given for only 4 or 5 days in succession. After its administration has been discontinued for a few days, it may be administered again and then stopped as soon as possible.

Tincture of iodine (7 per cent tincture of iodine USP XII) can be given in doses of 10 to 15 minims (0.6 to 1 cc) in a glass of water after meals. It usually should not be administered longer than a week but if it seems to help in reducing the number of rectal discharges and results in general well-being its administration may be resumed after a rest period of a week.

Among the sulfonamide drugs which have been found useful in the treatment of this disease are azosulfamide (disodium 4-sulfamido-phenyl-2-azo-7-acetylamino-1-hydroxy naphthalene-3,3'-disulfonic acid) and various derivatives of sulfathiazole. These drugs preferably should be administered in courses. After the drug has been administered for 2 weeks, its administration should be discontinued for one week. At the end of this period, the administration of the drug should be started again and continued for another 2 weeks. When azosulfamide is administered in this manner to an average adult, 60 to 90 grains (4 to 6 gm) of the drug can be administered in divided doses in 24 hours. For children the dose will be correspondingly smaller. Phthalylsulfathiazole (2-N-phthalyl sulfamylamido-thiazole) may be given in doses of from 120 to 240 grains (8 to 16 gm) in 24 hours.

VACCINE When improvement occurs, and in cases in which the disease is mild or is observed early, a bacterin, prepared as an autogenous vaccine from the organisms found in the rectal ulcers in each case, is administered subcutaneously. This is given every 3 to 5 days for several months. The initial dose is 0.1 cc and each succeeding dose is increased 0.1 cc until the patient is receiving 15 cc. After a rest of several months, the same procedure is repeated. Three or four such courses of treatment are administered, or the vaccine is given until the patient is free of symptoms. After that an occasional course of vaccine is given for several years.

NURSING CARE Most of the patients who have this type of colitis are so ill that hospitalization is advisable. Rest in bed usually is prescribed for the initial part of the treatment, and often for weeks during an acute exacerbation. The systematic execution of the many details necessary for comfort and peace of mind, as well as for actual physical progress, can be accomplished only by careful nursing which may be by the hos-

Although the toxicity of both of these drugs is low toxic reactions have been known to occur even with these sulfonamides. When either of these drugs but particularly the former is being administered it is important to have the concentration of hemoglobin the erythrocyte count and the leukocyte count checked frequently since anemia is likely to occur without other symptoms of toxicity.

Although sulfathiazole usually is well tolerated when a total dose of 45 to 75 grams (3 to 5 gm) is administered daily it is more likely to produce toxic effects than azosulfamide or phthalylsulfathiazole.

Since it has been observed that rheumatic fever and severe ulcerative colitis are similar in some respects various preparations of salicylic acid have been administered in the treatment of ulcerative colitis. Investigators have tried to prepare combinations of the sulfonamide drugs and preparations of salicylic acid. Salazopyrin (salicyl azo sulfapyridine) is an example of such a combination.*

Salazopyrin is given in divided doses in the same way as the other sulfonamide drugs are administered.

In cases of acute fulminating ulcerative colitis some of the other sulfonamide drugs such as sulfadiazine are indicated. They should be administered in suitable concentrations so that a concentration of at least 12 to 15 mg of the drug per 100 cc of blood will be maintained. A striking effect has followed the administration of all of these drugs in selected cases. The best results will be obtained when the administration of the drug is started early in the course of the disease.

Several antibiotics have received a clinical trial in cases of active ulcerative colitis. The only one that has proved useful in the treatment of this disease is penicillin. It is chiefly of value in cases in which the patients are very ill. In many cases in which the disease has been acute and has caused a high fever the passage of many bloody purulent stools

rapid wasting and all the concomitants of a severe debilitating illness the intramuscular administration of 50 000 to 60 000 units of penicillin every 3 hours has resulted in dramatic control of the symptoms. The administration of penicillin should be continued for at least 10 days to 2 weeks. As much as 100 000 units of penicillin has been administered every 3 hours by the intramuscular route in the treatment of some patients. Recently a few patients have received the calcium salt of penicillin by the oral route. Likewise on occasion penicillin in the form of rectal suppositories has been used. To date the latter two methods of administration have proved of little or no value in the treatment of the seriously ill patients.

Up to the present streptomycin has not proved of value in the treatment of this infection.*

OXYGEN. With the advent of the BLB mask which made it possible to administer oxygen in concentrations up to 100 per cent in an easy manner efforts were made to control the critical stage of this disease with oxygen. In a few cases the administration has produced immediate relief which has been striking. From a severe toxic state with high fever rapid thready pulse and cyanosis the patient's condition has been changed to one of comfort with temperature receding and fingers returning to normal color. All in all results parallel to those obtained in pneumonia have been achieved now and then.

TRANSFUSION OF BLOOD. In some cases the value of blood transfusions is inestimable. Blood may be given for several reasons: (1) in cases of severe sepsis and depletion to fight the toxemia; (2) for anemia and the weakness following loss of blood; (3) for hypoproteinemias; and (4) for general debility from longstanding disease. Two to five transfusions of 150 to 250 cc each, have

IRRIGATIONS AND INSTILLATIONS. Our experience as well as that of many other clinicians

* Since this article was written the use of the adrenocortical hormone ACTH has been found to be of definite value in this type of ulcerative colitis. The exact dosage remains to be determined as he and individualized for each patient.—Editor

* This drug is manufactured by A B Pharmacia Stockholm Sweden

is that the benefit which may be produced by the use of so called disinfecting irrigations is offset by the irritation they cause. It is essential to remember that no matter what the disinfectant may be one cannot hope by giving it as an enema to eradicate the infection. The disease extends deeply through all the layers of the bowel and it times into the mesentery and even into the blood stream. Consequently the most that can be accomplished by intestinal irrigation is cleansing of the surface and that only for a few minutes. In cases in which there is much perianal infection as there is in cases in which a fistula is present irrigation of the rectum with warm physiologic salt solution has made the patients comfortable. In the few cases in which such irrigations seem indicated physiologic salt solution is as useful as solutions of silver nitrate, mild silver protein, ichthamine or any of the many other drugs that have been used for this purpose.

In the case of a massive hemorrhage 3 to 4 oz (90 to 120 gm) of starch mixed with warm water and made into a thick paste so that it just flows and can be instilled into the rectum has been known to stop such a hemorrhage. One grain (0.065 gm) of powdered opium may be added to the suspension.

REMOVAL OF FOCI OF INFECTION Foci of infection should be removed if possible for they may serve as depots from which infection of the bowel may arise. If one wishes to do everything possible one should remove teeth that have periapical abscesses and suspicious looking or definitely infected tonsils. The tender and inflamed rectal wall usually will prevent the massage necessary to clear up prostatitis. Perianal infections, cryptitis and pyelitis should be treated cautiously. In general it can be said that foci of infection should be removed in the stage of remission or at least in the quiescent stage of the disease.

PARENTERAL ADMINISTRATION OF FLUIDS Since the patients frequently are seriously ill it is often necessary to administer fluids parenterally. The solutions used are (1) physiologic solution of sodium chloride 9 gm of sodium chloride per liter (2) Ringer's solution 9 gm of sodium chloride 0.24 gm of calcium chloride 0.42 gm of potassium chloride 0.20 gm of sodium bicarbonate in

1000 cc of triple distilled water (3) duodenal replacement formula (DR) 70 gm of sodium chloride 0.90 gm of potassium chlo-

sodium lactate 12.0 gm of sodium chloride 0.8 gm of potassium chloride 0.4 gm of calcium chloride in 2 liters of water. The main constituent of all of these solutions is sodium chloride in a concentration which is isotonic or slightly hypotonic when compared with the concentration in the blood. The last three solutions contain other ions which are helpful but perhaps of secondary importance. Two other solutions used for parenteral administration are a 5 or 10 per cent solution of dextrose in distilled water or in physiologic solution of sodium chloride.

The indications for parenteral administration of fluids are (1) dehydration (2) maintenance of water balance mineral balance

logic solution of sodium chloride over and above that needed to replace abnormal loss of fluid should be given in 24 hours. In cases of severe chronic ulcerative colitis in which the value for the plasma protein is low even this amount is excessive since that extra sodium chloride tends to produce edema rather than to correct the acidosis or alkalosis.

Surgical Treatment The problem of when operation should be performed arises often when one is dealing with this disease. There was a time when operation was thought desirable whenever the patient did not respond promptly to medical care. As a result of this opinion in many cases of the fulminating form of ulcerative colitis intestinal stomas were established in the hope that drainage of the fecal contents through the abdominal wall away from the diseased segment of bowel might allay the activity of the disease and permit healing. The high mortality rate accompanying surgical intervention has discouraged operation for this phase of the disease.

Intractability has been considered a definite indication for an abdominal intestinal stoma. Men of considerable surgical experience postulated that this infectious process

reached a stage at which the changes were irreversible and that when the disease reached this stage an intestinal stoma or perhaps even colectomy was indicated. In some instances this was probably true but I have not been able to find the man who can even approach an expression of the time when a disease process has become irreversible.

There is however a group of lesions which are inclined to occur as late sequelae of the disease and which definitely are surgical problems. The principal ones are polyps, neoplasms, strictures, extensive perianal fistulas, localized perforation and abscesses of one kind or another. Except for these complications and for acute intercurrent surgical disease, surgical treatment should be used sparingly.

The hope has recurred frequently that cure of this disease might be obtained by deflecting the current of intestinal content out of the abdomen. Various methods of doing this were tried. Ileostomy was found to be the procedure of choice. When ileostomy becomes necessary for complications it is usually performed when the patient's condition has become generally satisfactory. Then it can be performed with reasonable safety. Ileostomy has been employed in about 55 per cent of the total number of cases of thrombo ulcerative colitis in which the patients have been treated at the Mayo Clinic.

Cattell has put the problem of some of the patients suffering from this disease aptly when he said that "ileostomy is the price that some patients must pay for life" although he considered the disease primarily a medical problem.

It becomes obvious that when the disease has reached the stage at which ileostomy is advisable, colectomy should be performed at a later date but as soon as the patient's condition warrants. Usually it is well to postpone colectomy for at least 6 or 8 weeks after ileostomy has been performed.

These observations lead one to the inevitable conclusion that if and when thrombo ulcerative colitis has reached the stage at which operation seems indicated, ileostomy and subsequent colectomy would seem to be the procedures of choice. Only occasionally will healing subsequent to ileostomy be such

as to warrant later closure of the stoma. However it must never be forgotten that after ileostomy medical management should proceed in the manner employed before the operation was performed. If this is done carefully there will be a few cases in which the stoma can be closed reasonably safely later on.

In only a few cases has it been possible to close an iliac stoma once made for this form of chronic ulcerative colitis. From his observations the writer can say that such a stoma probably was established when the disease was not very extensive. When a stoma once has been established in cases of this disease it generally can be considered a permanent affair and colectomy will be come advisable as a subsequent surgical procedure.

With the current wave of enthusiasm concerning vagotomy for peptic ulcer it was natural that this operation would be tried for the control of the diarrhea of ulcerative colitis. The thought was advanced that a severance of the vagus nerve would interfere with the gastro ileal reflex. In a few patients with mild forms of ulcerative colitis this has been so. Whether this justifies an operation of such magnitude will be for the future investigators and students of the problem to decide. Vagotomy has not been helpful when ulcerative colitis has reached a fairly advanced stage, in fact in some patients of this type who were vagotomized there occurred a great increase in bowel activity and an intractable diarrhea resulted.

Prognosis—Although the present treatment of thrombo ulcerative colitis leaves much to be desired, a distinct advance has been made over other previous and contemporary endeavors. Thrombo ulcerative colitis must be considered somewhat as tuberculosis is considered, namely as a regressive destructive inflammation of the large intestine in which to stem the tide many measures must be brought into play and the patient as well as the physician must learn to undergo long suffering and to have patience.

The life span of patients who have thrombo ulcerative colitis may be materially shortened by the ravages of the disease. The experiences related in previous paragraphs clearly indicate how devastating this malady can be and how it can relegate a healthy

robust person slowly or relatively quickly to chronic invalidism and intense suffering. They also reveal that by careful continuous management a person so condemned can be restored to normal health and usefulness and they suggest that once a patient has had this disease he may have to adapt his future mode of living for years to restrictions imposed on him by the fact that he is a potential colitis patient.

Factors such as infection of the upper part of the respiratory tract, physical fatigue, marked nervous fatigue and anxiety states have been found to predispose to the disease. Similar factors may initiate relapses once the condition has been controlled.

It has been found that with the passing of time more and more patients are making a satisfactory recovery and are being restored to a useful life.

Although the results are not so striking in the fulminating type of the disease as they are in other types, even here great progress has been made and whereas only a few years ago nearly all the patients who had this type of the disease succumbed, now most of these patients are saved and once their symptoms are controlled the patients usually remain well.

The question might well be asked "What type of person can best withstand the disease and at what age do patients tolerate the disease best?" Here an apparent paradox exists. Children who are less than 12 years of age withstand the disease poorly and the percentage of such children who recover after the disease has caused much damage is relatively small. Although the disease is particularly devastating when it occurs in childhood, this does not preclude the living of a normal span of life by a child so afflicted and my experience indicates that when a patient has survived the first years of the onslaught of the disease the tendency in general is that the disease becomes milder or perhaps the patient becomes progressively better able to tolerate the condition. On the other hand, if the disease begins when the patient has passed the age of 60 years, the proportion of recovery is the greatest and approaches 100 per cent. As in most severe chronic infections, however, the onset is commonly in the second and third decades of

life. These patients usually are extremely ill yet the high percentage of satisfactory recoveries among them illustrates that unrelenting effort to control the disease is worth while. Once the patients have recovered and remain free of relapses, their longevity should not be affected by the fact that they have had the disease.

In that group of patients in which the onset is insidious and even among those cases in which the disease is severe from the onset, the tendency is for the first attack to be mild and of short duration for the second attack to be less mild and of longer duration and for the next attack to be more severe and more intractable with remissions between attacks becoming shorter and shorter until the patient is in continuous trouble. Furthermore, after an adequate program of management has been established, remissions become longer and exacerbations become progressively less severe and of shorter duration if they occur at all until finally the patient remains free of symptoms. This thought must be impressed on the patient so that he may not become discouraged and will follow an established program without interruption and without trying to take short cuts. What has been said here can be said about the patient for whom ileostomy becomes advisable.

It should be remembered that even though the active symptoms of the disease may have subsided, a patient must not relax his vigilance. If vigilance is maintained, results may be excellent. Again it may be said that there is an analogy between the course of this disease and that of tuberculosis and every patient who has had a severe attack of ulcerative colitis is a potential colitis patient. Relapses are common if these matters are not borne in mind. The most common causes of relapse are (1) infection of the upper part of the respiratory tract, (2) mental and physical trauma and (3) the lighting up of distant foci of infection.

J. ARNOLD BARGEN

REFERENCES

- Cattell H B Surgical Treatment of Ulcerative Colitis *Lahey Clin Bull* 12 1939
 Dennis C Eddy F D and Westover H Vagotomy in Treatment of Idiopathic Ulcerative Colitis and Regional Enteritis *Minnesota Med* 31 253 1948

REGIONAL (SEGMENTAL) ULCERATIVE COLITIS

The regional form of ulcerative colitis is one of the least common varieties. Various authorities have found that it comprises between 3 and 5 per cent of any large series of cases of ulcerative colitis. It presents the most bizarre picture, has the least clear cut manifestations, and offers the greatest diagnostic difficulties of any of the various types of colitis.

No common etiologic agent has been found for regional ulcerative colitis. One could think of this form as the problem child of colitis and if, as some insist, the term "non-specific" is to be applied to some forms of ulcerative colitis, it could be applied to this one. In this form of colitis more than in any other, we depend on the roentgenologic examination of the large intestine.

Treatment. It has been accepted generally that resection of the diseased segment of the bowel is the preferred treatment of regional ulcerative colitis. However, when to operate and which patients may be restored by medical measures remain unsettled problems.

One can say with a great degree of certainty when not to operate. It is unwise to explore the abdomens of these patients during the acute stage of the disease. Attempts at resection at that time are fraught with unnecessary risk. However, it is well to place the patient at rest in bed and provide all the supportive treatment available. Intravenously administered fluids, blood transfusions, low residue diets, and the judicious administration of sulfonamides have helped many a patient through the active stage of the disease. Sulfasuxidine and sulfathaladine have been particularly efficacious; the latter being the drug of choice. 120 to 130 grains (8 to 12 gm) are administered daily in divided doses. Furthermore, such complete relief of symptoms frequently has been

achieved by these supportive measures that resection was later deemed unnecessary. We can now say that many of these patients respond to medical measures.

If, however, so much damage to the intestinal wall has occurred that there is a severe persistent deformity, as depicted by roentgenologic study, resection is inevitable. Relief of this condition may be accomplished by exteriorization of the involved portion of the colon, or by colocolostomy, or ileocolostomy, and subsequent resection.

A well ordered program of preoperative care is of greatest value in these cases. This may result in a recession of acute symptoms and the patient's ability to withstand surgery may be immeasurably improved. Sulfasuxidine administered in divided doses to total 240 grains (16 gm) the first day and at the rate of 60 grains (4 gm) every 4 hours for 4 to 6 days before surgery, or sulfathaladine at the rate of 120 grains (8 gm) in divided doses during each 24 hour period, has been most helpful. In some cases the addition of streptomycin has been indicated. By and large the sulfonamides represent the preoperative drugs of choice, however, occasionally a patient's sensitivity to these drugs forbids their use, and in these cases and for some of the more seriously ill patients streptomycin is particularly helpful. About 2 gm of the latter should be given in divided doses each 24 hours. Saline aperients and cleansing enemas should also be given until the day of surgery so that the intestine is well cleaned before surgery is undertaken. A residue-free diet, especially high in carbohydrate, is helpful in preoperative care.

Complications. The major complication in these cases is colonic perforation. This may necessitate temporary colostomy pro-

allow several months to intervene between several stages of this procedure. Other complications common to thrombo ulcerative colitis have been encountered in this disease as well, principally those in which there

* Chloromycetin and aureomycin may prove to be of value in regional ulcerative colitis. Specific information as to their effectiveness in this condition is not available at the time of this writing.—Ed. tor

were systemic manifestations, that is, arthritis erythema nodosum, neuritis, infection of the urinary tract, phlebitis and deficiency states late in progressive infection. Stricture of the bowel has occurred, hemorrhage has occurred rarely but perirectal abscess fairly frequently. Since most of these complications demand individual attention, it would be difficult to lay down rules for the treatment of any one of them. It should be emphasized, however, that if perirectal abscess occurs in the presence of diarrhea, it is important that careful investigation of the intestine above the rectum be carried out. Disease in the intestine proximal to the rectum should be controlled before operation on perirectal infections and fistulas, except in cases in which it is necessary to operate immediately, as for drainage of an abscess or to institute measures for control of anal discomfort.

J. ARNOLD BARGEN

FUNCTIONAL DISORDERS OF THE COLON

Physiologic Principles. Functional disorders of the colon are characterized physiologically by hyperirritability of the neuromuscular mechanism of the bowel resulting from local mechanical or chemical irritation or from excessive stimulation of the autonomic nervous system. The dysfunction of the colon may consist of hypertonicity with irregular and intermittent spasm, hyperperistalsis or both. The abnormal muscular contraction, localized distention and increased smooth muscle tension of the bowel lower the threshold for visceral pain and thus cause abdominal distress of varying type and severity. The disturbed motility of the colon interferes with the normal rate of progress of fecal material, resulting in either constipation or diarrhea. In order to treat these patients satisfactorily, it is necessary to keep firmly in mind certain fundamental physiologic principles and not to be misled by the varying notions regarding bowel function so common among the laity. Gastric emptying takes place in a rather uniform time, one to 7 hours depending on the size of the meal. The transit of food through the small intestine, where digestion takes place, also occurs in a rather constant time, 2 to 4 hours. In the colon, however,

the rate of travel is much slower and more variable, the transit time ranging from a few hours to several days. The essential function of the colon is not digestion, but the absorption of water and the condensation of the watery small intestinal content into a formed stool for infrequent convenient evacuation. The desire to defecate is a conditioned reflex induced by the passage of fecal material from the descending colon and sigmoid into the rectum, by sitting on the toilet, by eating a meal (the gastrocolic reflex), by smoking a cigarette, or in various other ways.

Normal defecation consists of a well formed collection of feces, an inch or so in diameter, several inches in length, and firm in consistency. The spasticity of the irritable colon may induce prolonged retention of fecal material, excessive quantities of water may be absorbed and the feces evacuated as hard dry balls or as narrow, ribbon like masses. Constipation may result also from atony of the bowel and insufficient muscular activity, as in debilitated or elderly individuals but this type of constipation is not ordinarily accompanied by abdominal pain. Consequently, the passage of hard dry feces especially in the presence of abdominal distress usually signifies excessive spasm and too much irritation rather than too little. Soft unformed watery evacuations are indicative of hyperperistalsis, the feces traversing the colon too rapidly to permit the normal absorption of water.

The presence of excessive amounts of mucus is of some significance for mucus is secreted through the digestive tract in response to irritation, the more pronounced the irritation, the more mucus in the feces.

The etiologic factors in functional disorders of the colon are of two general types: (1) physiologic, direct stimulation of the neuromuscular mechanism of the bowel by mechanical or chemical irritants, and (2) emotional or psychologic, mediated by the autonomic nervous system. The physiologic causes include the immoderate consumption of irritating and laxative foods, excessive smoking, and the habitual use of laxatives, cathartics or enemas. The emotional or psychologic components seem usually to arise from the many small continued anxieties and frustrations of life, rather than from specific precipitating events, although in some cases

a direct cause and effect relationship may be apparent. Bad childhood habit patterns, emotional and intestinal, are often present and seem to result in a "conditioning" or "sensitization" of the colon. The disordered function of the bowel may thus be attributed to a hypersensitive neuromuscular mechanism, resulting from emotional stress, bad habit patterns, and similar nervous factors, plus the physiologic irritation of cathartics, enemas, highly laxative foods, and other poorly tolerated dietary practices.

Treatment. Treatment requires an accurate appraisal of the physiologic factors involved and careful evaluation of the patient as an individual. While the specific procedures employed should be adjusted to the requirements of each patient, certain principles are almost invariably applicable.

REASSURANCE. It is important initially to relieve the patient's anxiety concerning the possible presence of serious organic disease. This is accomplished most effectively by a thorough investigation comprising a careful history, complete physical examination, including digital examination of the rectum, proctosigmoidoscopy, blood count, urine analysis, examination of the feces for occult blood and parasites and roentgen examination of the digestive tract. The manner of informing the patient of the results of the study is of some consequence. It should be done with a calm, firm, cheerful, and secure attitude, not with too much pomp and circumstance, nor with great levity and casualness. The examination is of great concern to the patient; he should be reassured rather than frightened or belittled. The verdict of "no organic disease" must be followed by some explanation of the mechanism of the distress. Injunctions to "forget it, it is all in your head," etc., are ineffective; they constitute poor psychotherapy and poor medicine. Terminology is of some importance in this respect for the various names may have specific connotations for different patients. "Colitis" is often confused with ulcerative colitis. "Mucous colitis" may be regarded as an inflammatory disease of the bowel. "Spastic colitis" may be envisioned as an intense intractable spasm. "Nervous indigestion" may be interpreted as tantamount to an imaginary disease or a disturbed mind. The patient should be reassured that while

irritability of the colon is a common cause of abdominal distress, it does not lead to serious consequences. This form of superficial psychotherapy usually suffices; occasionally, a more complete analysis of the patient and his problems by a trained psychiatrist is required.

REST AND EXERCISE. Rest is of definite value, although the amount required depends on the severity of the disturbance and the circumstances present. In the average patient, long hours of sleep at night and a rest period during the afternoon are adequate. Some individuals benefit greatly from a vacation away from home and the problems of their daily routine. Patients with severe abdominal pain may require complete bed rest in the hospital for a period of several weeks. On the other hand, in some individuals exercise is helpful; it should not be too strenuous and it should provide pleasure.

HEAT TO ABDOMEN. In most instances, the application of heat to the abdomen in the form of an electric pad or a hot water bottle seems to quiet the hyperactivity, reduce the flatulence, and relieve the abdominal discomfort. Heat may be applied continuously, or on alternate hours, or for an hour or two after each meal, depending upon the severity of the distress. A hot bath, preferably in a tub, is often helpful.

ANTISPASMODICS AND SEDATIVES. The drugs of greatest value are the antispasmodics and sedatives. Tincture of belladonna, a time-honored remedy, may be prescribed in doses of 10 or 15 drops (0.6 to 1.0 cc) three or four times daily. Atropine sulfate, $\frac{1}{320}$ or $\frac{1}{160}$ grain (0.0005 or 0.001 gm) may be given by mouth three or four times daily, or $\frac{1}{80}$ grain (0.001 gm) may be administered

intracutaneous and to produce fewer side effects, appear to be of questionable superiority.

Barbiturates promote rest and sleep, relieve anxiety, and decrease intestinal hyperactivity. Phenobarbital in doses of 0.015 or 0.03 gm may be given three or four times each day. An effective prescription combines in tablet form phenobarbital 0.03 gm and extract of belladonna 0.0075 gm. When insomnia exists, the phenobarbital may be given in a single dose of 0.1 gm at bedtime.

Other preparations such as seconal (0.1 gm) or occasionally chloral hydrate (1 to 2 gm) may be substituted if preferred. Bromides may provide equally satisfactory relaxation but their use should not be prolonged because of the hazards of bromoderma or bromidism. Opiates are rarely needed and they are not desirable because they increase the tonicity of the bowel and also because of the danger of addiction. However, codeine sulfate 0.03 or 0.06 gm may be used occasionally for the relief of severe intestinal distress.

REGULATION OF INTESTINAL FUNCTION Patients should be educated to obtain satisfactory bowel movements spontaneously. Laxative preparations of all kinds including mineral oil, cathartics and large enemas are to be avoided. They increase the tendency to colonic spasm and pain and are unnecessary. This is true also of the relatively mild so-called bulk-producing substances although in general these are much less disturbing than the chemical laxatives. The elapse of several days or more without a bowel movement is of no consequence provided fecal material is not accumulating in the rectum. Most patients will recognize this sensation and will so inform the physician. The majority of patients will be alarmed at the passage of time without defecation and will ask for a laxative. The request should be denied and reassurance given but the rectum should be examined daily to make certain that a fecal impaction is not developing in the rectum. It is rare for impactions to form above the recto-sigmoid. Oil enemas may be given prophylactically when there has been no defecation during the entire day or when the stool has been hard and dry. Three or 4 oz of warm olive oil or mineral oil are instilled into the rectum by means of a rubber bulb type of ear syringe or by means of a small funnel and a large male catheter. The retention enemas may not be necessary or desirable but it is important to be on the alert for the development of such impactions. If a fecal impaction develops it should be broken up digitally and removed or evacuated by large enemas of tap water. Oil enemas are of no value for this purpose.

Laxatives and cathartics need not be prohibited under all conditions. Many patients

especially elderly persons for one reason or another develop the cathartic habit experience no distress or ill effects therefrom and may be permitted to continue the regimen they have found effective.

The act of defecation can be inhibited by neglect of the normal urge. The rectum gradually adapts itself to the bulk of feces and in time the desire to defecate may be lost completely. The importance of regular habits therefore should be emphasized.

may be used to stimulate the defecatory reflex when it is lacking and when the stool tends to collect in hard masses in the rectum. Glycerin suppositories also will be found effective for this purpose in many individuals.

Constipation may be further aggravated by anal spasm resulting from fissures or hemorrhoids; these conditions should be treated by appropriate measures.

DIET The dietary management is based on the varying laxative qualities of different foods (Table I). All food and drink is more or less stimulating to the digestive tract; there are however marked differences in quantitative and qualitative mechanical and chemical effects of various foods. The usual patient is best managed by prescribing a diet estimated to give the laxative effect required. It should produce firm formed stools rather than hard stools or on the other hand soft or liquid stools. A diet sheet should be supplied with specific instructions as to the foods to be eaten and those to be avoided. In practice a diet form such as the one outlined may be used; it enables the physician to delete easily certain foods or groups of foods. Since the abdominal distress and constipation are attributable to spasticity of the colon, the more irritating items in Sections 5, 6 and 7 of the diet are prohibited entirely. A fairly satisfactory procedure is that of permitting the patient to eat all of the foods in Sections 1 to 4 inclusive except for the more laxative cooked fruits and vegetables. The amount of cooked fruit and vegetable should be stipulated as perhaps two liberal (3 to 4 oz) servings of each daily. If the symptoms subside qualitatively and quantitatively additions to the diet

may be made. If the feces are hard and dry the intake of cooked fruit and vegetable is increased to three servings of each daily in patients with constipation and without abdominal distress the diet may be augmented by the addition of such foods as lettuce, celery and ripe tomatoes. The regimen is continued for several weeks or months or even longer if necessary. Indeed the majority of patients find it desirable to maintain some form of dietary restriction indefinitely.

The treatment of patients with diarrhea of functional origin is similar. Rest in bed, the application of heat to the abdomen and the use of phenobarbital and belladonna are helpful. Codeine (30 mg) may be given hypodermically together with 0.4 mg of atropine when severe pain is present. Paregoric, bismuth and similar preparations are of little value and indeed may aggravate the distress by increasing the tonicity of the bowel. In acute disturbances with severe diarrhea it may be desirable to omit all food for 24 hours and to administer 5 per cent glucose in isotonic saline solution intravenously. The first substances to be given should be hot water, broth, barley gruel and weak tea followed by oven-toasted bread, cream of wheat, boiled milk, cooked eggs, rice, custard and jello (Section I of diet). The diet is gradually expanded as improvement occurs. Excessively hot or cold foods should be avoided. Fruits and vegetables, both cooked and raw, are prohibited until the diarrhea has subsided and the stools are formed. The diet should be continued until the bowel function has been normal for several weeks.

There is usually no difficulty in selecting a menu adequate in nutritional requirements except in those patients with acute bowel distress who are able to tolerate only the foods listed in Section I. However, this restricted diet may be safely taken for the several days necessary for the acute symptoms to subside. The use of vitamins though unnecessary may be permitted.

Failure with the therapeutic program described is usually attributable either to an unrecognized organic disease or to a difficult unsolved psychiatric problem. In most instances the skillful application of the principles outlined brings to the co-operative

patient restoration of normal bowel function and a gratifying relief of symptoms.*

TABLE I

LAXATIVE EFFECT OF VARIOUS FOODS

(1) Foods with Minimal Laxative Effect and Hence Best Tolerated in Acute Disturbances

Water, weak tea, rice or barley gruel, meat broth, cream of wheat, farina, oven-toasted bread, zwieback, toasted soda crackers with butter, soft-cooked eggs, boiled milk, custard, plain jello.

(2) Most Substantial But Relatively Bland and Easily Digestible Foods

Cereals with milk or cream, refined rice, rice Krispies, puffed rice, puffed wheat, corn flakes, oatmeal (well cooked).

Soups: consommé, strained chicken broth, strained vegetable, strained cream of rice, strained cream of potato, strained cream of celery, strained cream of mushroom, cream of tomato.

Cheese: cream, American, Swiss, cottage.

Fish: salmon, tuna, whitefish.

Poultry: chicken, turkey, squab.

Meats: beef, veal, lamb, ham, liver (broiled, boiled, roasted or baked).

Miscellaneous: crisp bacon, macaroni, noodles, spaghetti, vermicelli.

Potato: baked, mashed, au gratin or escaloped.

Breads: white, toast, croutons, bread sticks, milk toast.

Milk products: milk, cream, butter.

Other beverages: tea, coffee, postum.

Desserts: custards, vanilla, caramel, rice

puddings, bread, tapioca, cornstarch, cottage

snow, cakes, angel food, icebox, plain, sponge

cookies, arrowroot, hydrox, Peter Pan, vanilla

wafers.

Pies: lemon, cream, custard, banana, cream.

(3) Cooked or Canned Vegetables More Laxative Chiefly because of Greater Residue

(a) Moderately irritating: asparagus, string beans, carrots, spinach, sweet potatoes, peas, beets, tomatoes, squash.

* Methylcellulose has been advocated by Barger.

"... with a laxative dose of 4 tablets before each meal and at bedtime.—Ed tor Barger, J. A. A Method of Improving Function of Bowel. The Use of Methylcellulose. *Gastroenterology* 13:275, 1949.

- (b) More irritating artichokes parsnips
onions cabbage cauliflower rutabaga
eggplant green peppers turnips kohlrabi
broccoli navy beans lima beans corn
- (4) *Cooked or Canned Fruit More Laxative because of Chemical Irritants*
(a) Prunes peaches applesauce apricots
pears baked apple cherries
(b) Figs plums dark cherries berries grapes
pineapple rhubarb
- (5) *Raw Vegetables More Laxative*
Lettuce tomato celery watercress endive
radishes onions cucumbers cabbage
- (6) *Raw Fruits More Laxative*
Banana (least laxative) oranges (juice sections whole) grapefruit apples melon pineapple berries of all kinds pears peaches cherries grapes plums apricots avocado pear
- (7) *Miscellaneous Foods Some Very Laxative such as Honey and Beer*
Icecream with fruit or nuts syrup molasses
honey popcorn candy nuts pickles olives
relishes catchup spices various seasonings
buttermilk French fried potatoes raisin
bread soft or carbonated drinks coca cola
ginger ale sodas cider
Alcoholic beverages beer whiskey wine etc
WALTER L PALMER
JOSEPH B KIRSNER

REFERENCES

- Alvarez W C *Nervousness Indigestion and Pain*
New York P B Hoeber 1943
- Alvarez W C *An Introduction to Gastroenterology*
New York P B Hoeber 1948
- Palmer W L *Irritable Colon in Cecil's Textbook of Medicine*
Philadelphia W B Saunders Company 1948
- Palmer W L *Functional Disturbances of Alimentary Tract*
M Clin North America 28 418 1944
- Palmer W L *Functional Bowel*
M Clin North America 22 139 1938
- Peters G A and Bergen J A *Irritable Bowel Syndrome*
Gastroenterology 3 399 1944
- White B V Cobb S and Jones C M *Mucous Colitis Psychological and Medical Study of Sixty Cases*
Psychosomatic Medicine Monographs No 1 p 103 Washington D C 1939

DIVERTICULOSIS AND DIVERTICULITIS

The formation of diverticula cannot be prevented nor can diverticula be made to disappear. While diverticulosis per se does not cause symptoms and therefore requires no treatment it is often accompanied by irritability of the colon and alleged constipation. The treatment is the same as that outlined for functional disorders of the bowel. Laxatives cathartics and enemas are

irritating and should not be used routinely. In some patients small amounts of mineral oil (15 to 30 cc) given by mouth are well tolerated but in others the symptoms are aggravated. The rectal instillation of 3 or 4 oz of warm mineral oil or olive oil facilitates the elimination of hard dry feces. Tincture of belladonna 10 to 15 drops or atropine sulfate 0.0005 to 0.0004 gm may be prescribed before meals and in the evening. Phenobarbital in doses of 0.03 gm may be given four times daily.

Diverticulitis most often involves the sigmoid or descending colon because of the higher incidence of diverticulosis in this region and the smaller caliber of the bowel. The formation within the diverticula of small hard fecal masses may serve as foreign bodies and precipitate an infection. Acute diverticulitis in the majority of instances responds to conservative treatment including rest in bed, the application of heat to the abdomen and the avoidance of laxatives and enemas. The diet initially may be limited to warm liquids or soft food.

Large amounts of food may be held by mouth for several days and to administer 5 per cent glucose in isotonic saline solution intravenously. Mineral oil softens the stool facilitates its evacuation and may be given by mouth in daily quantities of 30 to 60 cc. Retention enemas of mineral oil or olive oil are similarly helpful. Sulfasuxidine 2 gm every 4 to 6 hours may help to control infection within the lumen of the bowel. If high fever and marked leukocytosis are present the administration of 30,000 to 50,000 units of penicillin every 4 hours may be necessary. One or 2 gm of dihydrostreptomycin every 24 hours may aid in controlling an infection that is not responsive to penicillin. Aureomycin or chloromycetin 250 to 750 mg every 6 hours may prove to be valuable agents in patients with severe infections.

Obstruction may occur as the result of inflammatory edema and fibrosis. Conservative treatment is effective.

than it is in obstruction of the small intestine nevertheless may be utilized for decompression of the bowel. Persistent obstruction may

necessitate the establishment of a colostomy in the transverse colon or the cecum. With the fecal current thus diverted the diverticulitis and the obstruction in some cases subside completely or at least sufficiently to permit resection of the diseased segment of the intestine.

Diverticulitis may progress to acute perforation with local peritonitis, chronic perforation with the formation of a peridiverticular abscess or rarely spontaneous rupture of an inflamed diverticulum into the free peritoneal cavity. Acute perforation of course requires immediate operation; the procedure after the abdomen has been opened will depend on the findings and the preference of the surgeon.

Chronic perforation with the formation of an abscess is except for chronic obstruction the most common complication of diverticulitis. Conservative nonoperative treatment with chemotherapeutic agents, antibiotics and other supportive measures may be attempted for several days in the hope that the abscess will resolve spontaneously. In the majority of cases it is necessary to incise and drain the abscess and to establish a colostomy. More radical surgery should not be undertaken at this time because of the danger of extension of the infection and because of the technical problems involved in dealing with inflamed and edematous tissues.

Perforation may occur into adjacent loops of bowel, the urinary bladder or the abdominal wall and result in the formation of permanent fistulas. The treatment is surgical and consists initially of a transverse colostomy or a cecostomy; diversion of the fecal current is particularly important in dealing

with a vesicocolic fistula to avoid the serious complication of an ascending infection of the urinary tract. More definitive therapy may be undertaken after an interval of several weeks or months, the fistula and the involved segment of a bowel are resected with end to end anastomosis and closure of the secondary openings of the fistulous tract. A further indication for resection is the inability to differentiate conclusively between diverticulitis and neoplasm.

Careful preoperative and postoperative treatment are necessary to reduce the operative morbidity and mortality to a minimum. The oral administration of sulfonamide drugs or streptomycin for several days before operation reduces the bacterial flora of the gut and lessens the possibility of serious infection. The principles of postoperative care are those of intestinal surgery in general: gastric suction, administration of antibiotics and fluids, the maintenance of nutrition and early ambulation.

WALTER L. PALMER
JOSEPH B. KIRSNER

REFERENCES

- Edwards H. C. *Diverticula and Diverticulitis of the Intestine*. Bristol, England: J. Wright & Sons, 1939.
- Johnson T. A. *Colonic Diverticula*, in: Bockus *Gastroenterology*, 2:674. Philadelphia: W. B. Saunders Company, 1946.
- Nash H. C. and Palmer W. L. Clinical Significance of Diverticulosis Including Diverticulitis of Gastrointestinal Tract. *Ann. Int. Med.* 27:41, 1947.
- Rosser C. and Kerr J. G. *Diverticulosis and Diverticulitis*, in: *S. A. Port's Diseases of the Digestive System*. Philadelphia: Lea & Febiger, 1944.

DISEASES OF THE LIVER AND BILIARY TRACT

TOXIC HEPATITIS

poisoning etc.) or may complicate other illnesses (pneumonia, septicemias, yellow fever, syphilis, amebiasis, malaria, dengue, infectious mononucleosis, etc.).

Treatment. Treatment consists of the following general measures:

Bed rest is most important. The patient should be kept at strict bed rest usually for 3 to 4 weeks or for one week after the following requirements have been satisfied: return of the liver to normal size (or if slightly enlarged it should be nontender and there should be an absence of symptoms), icteric index below 20 units and the total serum

bilirubin below 25 mg per cent, and the bromsulfalein retention below 10 per cent in one hour (5 mg per kilogram dose). Return of symptoms, enlargement of the liver, or tenderness over the liver area in a patient who has become ambulant necessitates prompt return to bed rest.

DIET The diet is as important as bed rest and should be high in protein (125 to 200 gm), and carbohydrate (300 to 400 gm) and moderate in fat (80 to 90 gm). High protein liquid feedings have been valuable in our experience to supplement the regular diet and also in patients who will not take solid foods. One of these may be made by adding 3 eggs, 4 oz of skimmed milk powder, and 6 oz of lactose to 1 qt of skimmed milk and flavoring to taste. Such a mixture will furnish 350 calories ($C = 49$ gm, $P = 20$ gm, $F = 8$ gm) per glass (240 cc). One hundred gm of protein hydrolysate (vipeptolac—Wyeth essenamine—Winthrop Stearns ledinac—Lederle etc.) may be substituted for the eggs and milk powder in the mixture above although usually they are less palatable and more expensive.

For patients unable to take adequate oral nourishment tube feeding may be resorted to. If this is not possible protein hydrolysates in glucose (amigen—Mead Johnson parenamine—Winthrop Stearns hyprotugen—Baxter) may be administered intravenously (2 or 3 liters daily will furnish 100 to 150 gm of protein hydrolysate). A normal diet may be resumed as the patient recovers and the jaundice subsides.

Fluid intake should equal 2400 to 2800 cc daily, except where there is oliguria, anuria or marked ascites. In such cases, fluids must be balanced with great caution to prevent overhydration or dehydration and as a general rule, to a basal level of 1200 to 1500 cc one may add an amount equal to the urinary output for the previous 24 hours to determine the total permitted. Fluids administered may be 5 per cent glucose in physiologic saline, especially if vomiting or acidosis is prominent protein hydrolysates (for nutrition), irradiated plasma, concentrated human serum albumin, or whole blood (for nutrition, dehydration and to combat shock). Where blood or plasma has been used, it might be wise to administer 10 cc of gamma globulin at monthly intervals for two or

three doses in an attempt to prevent homologous serum hepatitis.

Supplemental vitamin therapy may be given orally and parenterally and should furnish adequate amounts of vitamin A (5000 U.S.P. units daily) vitamin C (100 mg daily) and B complex (thiamine chloride 5 mg daily, riboflavin 4 mg daily, niacin or niacin amide 30 to 50 mg daily). Vitamin P (rutin) in doses of 50 to 300 mg daily may be given for purpura resulting from a deficiency of this vitamin. Vitamin K may

be given in doses of 3 to 5 cc three times weekly in doses of 3 to 5 cc three times weekly is a definite aid. Along these lines intraheptol (Lederle), an aqueous liver extract given intravenously, may be used as an adjunctive measure. Testosterone in doses of 25 to 100 mg three times weekly has been said to result in clinical improvement.

Oxygen is often used to combat cyanosis and anoxia, and we have employed antibiotics prophylactically to prevent pneumonia in very ill patients. For more intensive therapy of the acidosis that at times develops, the reader is referred to the section of

recovery in these cases. Management of ascites is discussed in the section on therapy of cirrhosis of the liver.

Specific forms of therapy may include (1) Removal of any hepatotoxic agents including those that may have precipitated the illness or contributed to it where the toxic hepatitis is secondary to some other infection, appropriate antibiotic therapy should be instituted (penicillin for pneumonia and syphilis, emetine and diodoquin for amebic

gm daily) should be employed where there is reason to suspect that fatty metamorphosis of the liver may be present (carbon tetrachloride and chloroform toxicity). In addition there is some evidence that choline may be more beneficial than methionine and that it may even be helpful where fatty infiltration is not demonstrable. (3) BAL (23

lumercaptopropanol) may be utilized where the toxic hepatitis is a result of arsenic or mercury poisoning. This drug is given in doses of 2.5 to 3.0 mg per kilogram body weight every 4 hours the larger dose being employed in the more seriously poisoned patient. Six injections of this dosage are given on the first 3 days of treatment four on the third day and two injections daily from the fourth through the 10th days.

WILLIAM E. MOLLE
LESTER M. MORRISON

REFERENCES

- Best C H Maclean D L and Rudolf J H
Effect of Choline and Liver Fat in Phosphorus
Poisoning *J Physiol* 83 275 1935
- Brunschwig A Johnson C and Nichols S Car
bon Tetrachloride Injury of Liver Protective Ac
tion of Certain Compounds *Proc Soc Exper
Biol & Med* 60 389 1945
- Eagle H Systemic Treatment of Arsenic Poisoning
with BAL (2,3-Dimercaptopropanol) *J Ven
Dis Invest* 27 114 1946
- Kinsell L W et al Protein Balance Studies in
Patients with Liver Damage Role of Lipotropic
Agents *Ann Int Med* 29 881 1948
- Kunkel H G et al Use of Concentrated Human
Serum Albumin in Treatment of Cirrhosis of Liver
J Clin Investigation 27 505 1948
- Labby D H et al Intravenous Therapy of Cir
rhosis of Liver *JAMA* 133 1181 1947
- L
- Morrison L M Response of Cirrhosis of Liver to
Intensive Combined Therapy *Ann Int Med*
24 465 1946
- Ottenberg R and Spiegel R Present Status of
Nonobstructive Jaundice due to Infectious and
Chemical Agents Causative Agents Pathogene
sis Interrelationships Clinical Characteristics
Medicine 29 27 1943
- Patek A J Jr et al Dietary Treatment of Cir
rhosis of Liver *JAMA* 138 543 1948
- Rosenak B D Moser R H and Kalgore B Jr
Treatment of Cirrhosis of Liver with Testosterone
Propionate *Gastroenterology* 26 690 1947

ACUTE YELLOW ATROPHY OF THE LIVER

The results of therapy in acute yellow atrophy or acute diffuse necrosis of the liver as it is now known are disclosed by the fact that an essential point in the diagnosis of true acute atrophy of the liver is its fatal outcome (Lichtman). However, a substantial number of these cases has been reported in the literature wherein recovery was

claimed following treatment. Many observers have asserted that such cases were actually subacute yellow atrophy of the liver or subacute diffuse liver necrosis and not true cases of acute liver atrophy. Since the same factors operate in both the acute and subacute varieties and the difference is only in the degree of liver involvement the treatment for both varieties is described.

Treatment of this disease requires heroic

is through the intravenous route. If the patient is able to take oral food or fluids at least 500 gm daily should be taken by mouth. Since most patients are too sick for this the intravenous administration of 10 per cent glucose should be given slowly at the rate of 250 cc per hour a total intake of 3000 cc will thus insure the intake of 300 gm of glucose or 1200 calories. In this way the urgent need by the liver for a sufficient supply of glucogen is met and the means provided for preventing the fatal hypoglycemia which may occur in these patients (Bockus). The total glucose intake 1000 cc should be in normal saline to insure adequate sodium balance. Next or equal in importance is the intravenous administration of protein. Probably the most efficient way of accomplishing this is through whole plasma in large amounts since the hepatic necrosis renders proper utilization of amino acids difficult. Irradiated plasma is preferable to reduce the danger of subsequent development of homologous serum hepatitis.

Intravenous methionine in 5 per cent solution has been reported of value in stimulating regeneration in these cases (Tumen). A 10 per cent solution in distilled water (500 cc) may be administered simultaneously with the intravenous glucose solution.

Vitamin B complex and vitamin K should also be given together with the above stated intravenous infusions. At least 50 to 100 mg of thiamine hydrochloride and 250 to 500 mg of nicotinamide should be incorporated in the intravenous therapy daily (Snell and Butt). Serious depletion of prothrombin usually is present. 10 mg of vitamin K should therefore be tried and included in the daily intravenous infusions. Unfortu-

prothrombin Hemorrhagic tendencies are therefore best combated by transfusions of whole blood (500 cc) until the blood prothrombin time approaches normalcy

Anemia is controlled by blood transfusions, if the anemia produces anoxemia this is best treated by the use of oxygen by an oxygen tent or through a B.L.B. mask Restlessness is most safely treated by the soluble barbiturates rather than by opiates which rely on the liver for detoxification

In the writer's experience pruritus may be controlled in about one third of the cases by the use of ergotamine tartrate, 1 mg three times daily by mouth, or subcutaneously once daily in from 1 to 3 mg dosage This drug however, can be toxic and must be observed carefully Rowntree found calomel useful in 15 to 3 mg dosage once every hour for four doses per day, without a saline purge for several days In completely intractable cases Wilbur has reported the successful use of intravenous procaine hydrochloride in dosage of 20 cc of 0.1 per cent solution, administered slowly

Hepatic coma has been reported as successfully treated in some cases by the daily intravenous administration of 5 gm lactic acid in 100 cc of normal saline solution (Epinger)

LESTER M. MORRISON

REFERENCES

Bockus H. L. *Diagnosis and Management of*

1942

Lichtman S. S. Therapeutic Response to Ergotamine Tartrate in Pruritus of Hepatic and Renal Origin *J. A. M. A.* 97 1463, 1931

Rowntree L. G. Considerations in Cirrhosis of Liver *J. A. M. A.* 89 1590 1927, correction 89 2126 1927

Snell A. M., and Butt, H. H. Hepatic Coma, Observations Bearing on Its Nature and Treatment *Tr. A. Am. Physicians* 56 321, 1941

Turner H. J. Cirrhosis of the Liver in Bockus' *Gastroenterology* Philadelphia W. B. Saunders Company, 1946 Vol. 3, p. 293

Wilbur, D. L. Therapeutic Agents in Liver Disease, Review of Medicinal Agents *J. A. M. A.*, 134 598, 1947

PORTAL CIRRHOSIS OF THE LIVER

Cirrhosis of the liver is no longer regarded as a hopeless, incurable disease which progresses unchecked until death intervenes. Recently numerous reports have demonstrated that many patients with hepatic cirrhosis can improve or even recover as determined by clinical observations and laboratory tests following treatment to be described below The writer has reported a detailed analysis of the results of treatment of cirrhosis under controlled conditions in a series of some 100 patients studied over a 10 year period, the results of these studies revealed that an encouraging and growing number of patients had improved or recovered to the point where they were able to resume their work or household activities

The patient should be kept in bed at complete rest for several weeks until the acute phases of the disease have passed and substantial improvement has taken place

Diet The diet is one of high protein, high carbohydrate, and low fat content The daily maximal protein intake aimed at is approximately 200 gm, carbohydrate from 800 to 500 gm, and fat 50 to 75 gm in those patients able to take a full solid diet In the severely decompensated patient for whom a liquid diet is required, the caloric intake is necessarily low, but is increased to maximal tolerance as soon as possible Lean meat is eaten at least twice daily, skimmed milk and cottage cheese are taken in liberal quantities

Lipotropic Agents (Preventive of Fat Deposit) CHOLINE Choline in the salt form is administered, 1 gm, preferably divided as 1 tablespoonful (2 gm) after each meal three times daily Three choline salts are available, i.e., choline bicarbonate, choline chloride, choline dihydrogen citrate The bicarbonate and chloride salts can be administered in smaller volumes than the dihydrogen citrate salt

bicarbonate is best tolerated by the gastrointestinal tract, and least likely to upset the patient with gastro intestinal symptoms The

choline should be administered for periods of 1 month to 6 months in most cases depending on the clinical progress of the patient

METHIONINE Methionine has been recommended in the past as adjunctive therapy with or instead of choline if desired, in the divided dosage of 1 gm with choline. Methionine comes in tablet form and has been considerably more costly than choline, although used in the same way.

Recent studies in patients with cirrhosis by Kinsell et al have demonstrated the unequivocal effect of choline as a lipotropic agent in the treatment of patients with cirrhosis of the liver. The studies in these patients were based on the most careful nitrogen balance investigations plus liver function tests, ketosteroid estimations, blood chemistries and numerous other clinical and laboratory procedures. Choline was conclusively proved to be a valuable adjunct when added to a high protein diet in the therapy of human cirrhosis. However it cannot be expected to be of value in reversing the pathologic process involved in a case of terminal Laennec's cirrhosis or biliary cirrhosis as will be described below.

These conclusions drawn by Kinsell et al have recently been corroborated by Chaikoff et al in the cirrhosis of the liver induced experimentally in dogs. Chaikoff's group has demonstrated that in this disease under experimental conditions, the feeding of a

in addition to a high protein diet, the liver cirrhosis promptly disappeared and gave way to a normal liver.

Kinsell and his co workers have recently introduced information which demonstrates that in patients with chronic severe cirrhosis of the liver, methionine alone acts definitely as a toxic agent when administered in either oral or intravenous form. These investigators have based their conclusions on the results of nitrogen balance studies, and blood methionine levels. Morrison came to similar conclusions based on clinical observation and as a result in two previous communications on therapy of cirrhosis, abandoned completely the use of methionine alone in chronic cirrhosis of the liver.

LIVER EXTRACT A whole or crude liver extract is administered intramuscularly in a dose of 3 to 5 cc (together with novocain if needed for local pain) daily for 10 days, then every other day for 10 days, and subsequently two to three times weekly as indicated by clinical progress. The liver extract is reinforced by vitamin B complex so that each cubic centimeter of liver extract contains at least 10 mg of vitamin B, 0.3 mg of riboflavin, and 10 mg of nicotinamide. In addition, one capsule of a high potency multiple vitamin preparation is given three times daily. If parenteral liver extract cannot be administered, a useful substitute is prepared by the oral ingestion of 3 to 6 oz of a whole aqueous liver solution or filtrate in fruit or tomato juice before or during each meal. This should be taken with 2 teaspoonfuls of brewers' yeast powder three times daily, either with the liver solution or separately as desired by the patient. In those patients with an abnormal blood prothrombin time, vitamin K is administered orally, 5 mg with 5 grains of bile salts three times daily; parenteral vitamin K may also be administered in 10 mg dosage until the blood prothrombin time has begun or approached normal. If this fails to occur after from three to five injections, blood transfusions may be resorted to in order to improve the blood prothrombin time.

The oral administration of amino acids has been a useful therapeutic adjunct, provided large and adequate dosage is used. No alcoholic beverages are to be taken by the patient.

Prognosis On the basis of liver punch biopsies in a series of patients with cirrhosis treated by the author, the following prognostic guide is offered as to the successful outcome or failure of treatment in a given patient.

REVERSIBLE CIRRHOSIS OF THE LIVER Favorable prognosis following treatment is possible. Cirrhosis of the liver associated with nutritional deficiency in

- (1) Chronic alcoholism, early or moderately advanced stages
- (2) Chronic ulcerative colitis
- (3) Deficiency diseases
- (4) Diabetes mellitus

IRREVERSIBLE CIRRHOSIS OF THE LIVER Poor prognosis following treatment

- (1) Biliary cirrhosis
- (2) Cardiac cirrhosis, i.e., fibrosis of the liver following chronic cardiac congestive failure
- (3) Certain hepatic diseases such as Banti's disease, hemochromatosis, parasitic diseases (*Clonorchis sinensis*), etc
- (4) Cholangiolitic cirrhosis following chronic infectious hepatitis
- (5) Terminal stage of Laennec's cirrhosis (small, shrunken, fibrous liver)
- (6) Laennec's cirrhosis with superimposed acute necrotic and toxic hepatocellular destruction occurring as a terminal event (Certain cirrhoses such as syphilitic cirrhosis which is now so rare are not described here)

A consistent histologic finding in liver punch biopsies which has characterized the patients responding favorably to treatment of cirrhosis has been the presence of fatty or "reversible" infiltration and/or fatty degeneration of the hepatic cells. Those patients failing to respond to treatment have been usually those without fatty infiltration or fatty degeneration. These latter findings are characteristic of those cases formerly known as "alcoholic cirrhoses." It is now well known that in order to produce cirrhosis of the liver alcoholism must occur in the presence of a diet deficient in protein and in vitamin content.

Treatment of Ascites. This is done by intravenous liver extract, diuretics, paracentesis, or by surgical procedures. Recently intravenous liver extract has been employed with some success in the treatment of ascites where other therapy has not been successful. The intravenous liver extract (Intraheptol-Lederle) is given as a course in the following manner. First, allergic sensitivity to the liver extract is tested by the intramuscular injection of from 0.1 cc to 0.2 cc of the concentrated extract, as recommended by Ralli and Labby et al. Allergic reactions are rare. If no allergic reaction occurs within 30 minutes, a first intravenous dose of 1 cc diluted with 25 cc of saline or 5 per cent glucose solution is given slowly. The series of conservative, graduated doses are given as follows:

- | | | | |
|----------|------|------------|-------|
| 1st day— | 1 cc | diluted to | 25 cc |
| 2nd day— | 3 cc | " " | 30 cc |
| 3rd day— | 5 cc | " " | 40 cc |

4th day— 5 cc " " 40 cc

5th day—10 cc " " 50 cc

6th to 14th days—10 cc diluted to 50 cc thr
Subsequently 10 cc diluted to 50 cc thr
times a week

When there is improvement, it may not occur until after the lapse of several weeks; hence subsequent intravenous liver extract administration depends on the patient's progress, some patients have been maintained for 6 months on injections of the extract twice weekly. The first indication of clinical improvement has been improvement in appetite, followed by increase in weight and strength. The diuretics are given in the manner usually prescribed for heart disease. Paracentesis and the varied surgical procedures for medically intractable ascites are described in surgical texts for the relief of portal decompensation.

Bleeding Esophageal Varix. The treatment of hematemesis from bleeding esophageal varices calls for abstention from solid or semisolid food until the bleeding has stopped. Bland liquids at room or body temperature may be taken if the patient's condition warrants this, for example, milk, water, tea. When the hemorrhage has subsided the treatment is similar to that employed in a bleeding peptic ulcer. Following the cessation of hemorrhage and the establishment of the source of bleeding through esophagoscopy and roentgen examination the esophageal varices may be injected directly according to the technique of Crafoord and Frenckner and Moersch. One cubic centimeter of a 25 per cent solution is injected at 4 day intervals, requiring four or more injections in a course of treatment. Gradual obliteration of the varices may be produced in this way and may require repeated injections if recurrences are encountered. Successful results have been described in a number of cases following 5 year progress studies. This treatment is understood to be entirely symptomatic and is an adjunct to the treatment of the underlying disease.

LESTER M. MORRISON

REFERENCES

- Beams, A. J. Treatment of Cirrhosis of Liver with Choline and Cystine. *J.A.M.A.*, 130:190, 1946.
Brown, G. O., and Muether, R. O. Treatment of Hepatic Cirrhosis with Choline Chloride and D-
et

Low in Fat and Cholesterol *JAMA*, 118 1403, 1942
 rafoord, C., and Frenckner, P. New Surgical Treatment of Varicose Veins of Oesophagus *Acta otolaryng.*, 27 423, 1939
 ntenman, C., et al. Choline Prevents Fatty Change and Cirrhosis in Livers of Dogs Subjected to

Reference to Prognosis and Treatment *Am J Digest Dis* 9 115, 1942

insell L. W. Factors Affecting Protein Balance in the Presence of Chronic Viral Liver Damage *Gastroenterology*, 11 672 1943

insell L. W., et al. Protein Balance Studies in Patients with Liver Damage Role of Lipotropic Agents *Ann Int Med.*, 29 881, 1948

abby, D. H., et al. Intravenous Therapy of Cirrhosis of Liver *JAMA*, 133 1181 1947

moersch, H. J. Treatment of Esophageal Varices by Injection of Sclerosing Solution *J Thoracic Surg* 10 800, 1941

ornison, L. M. Evaluation of Treatment for Cirrhosis of Liver *Ann West Med & Surg.*, 2 143, 1948

ornison, L. M. New Methods of Therapy in Cirrhosis of Liver *JAMA* 134 673 1947

ornison, L. M. Response of Cirrhosis of Liver to Intensive Combined Therapy *Ann Int Med.*, 24 485 1946

Patek, A. J., Jr. Treatment of Alcoholic Cirrhosis of Liver with High Vitamin Therapy *Proc Soc Exper Biol & Med* 37 329 1937

Patek, A. J., Jr. and Post J. Treatment of Cirrhosis of Liver by Nutritious Diet and Supplements Rich in Vitamin B Complex *J Clin Investigation*, 20 481 1941

Ralli M. P., et al. Factors Influencing Ascites in Patients with Cirrhosis of Liver *J Clin Investigation* 24 316, 1945

Russakoff, A. H., and Blumberg H. Choline as Adjuvant to Dietary Therapy of Cirrhosis of Liver *Ann Int Med.*, 21 848, 1944

disease As shown by Havens, there are strong indications that medication with gamma globulin during the preicteric phase of serum hepatitis will prevent the disease in a high percentage of cases Ten cubic centimeters of gamma globulin are administered on two occasions, one month apart, starting one month after blood products were received, for children the dose has to be calculated on the basis of body weight, 0.08 cc per kilogram (Duncan)

Throughout the course of the disease, the daily diet should contain at least 150 gm of protein, 400 gm of carbohydrates, 125 gm

to increase the caloric intake and thus to avoid rapid loss of weight (Hoagland) No evidence has been submitted to substantiate the fact that increase of the protein content of the diet, or restriction of fat intake contributes to the success of therapy (Darmady) Anorexia, nausea, and vomiting, as they may be encountered during the early stages of the disease, require parenteral administration of 5 to 10 per cent glucose in isotonic sodium chloride (1000 to 2000 cc), the amount depending on urinary output, blood chloride and CO₂ levels Urinary output should be kept in excess of 800 cc during each 24 hour period Whenever a lowering of the plasma prothrombin level is observed, parenteral vitamin K (hykinone, 24 mg—Abbott), daily for 7 days, is prescribed Opiates and barbiturates are not well tolerated, and should therefore be used only sparingly

It is not advisable for the patient to resume his usual activities until the liver has ceased to be tender, has receded to normal size, or is at least no more than slightly enlarged and hepatic function has returned to normal, or is approaching normal The latter is best determined by means of the bromsulphalein test, using a 5 mg per kilogram body weight dose, the retention not exceeding 10 per cent after 45 minutes, the icteric index should show a value below 20 units In cases of acute suppurative hepatitis following obstructive jaundice, similar supportive therapy is advised preoperatively (Rosenthal) In amebic hepatitis the foregoing measures have to be augmented by

HEPATIC INSUFFICIENCY

(Liver Failure)

Acute Hepatic Insufficiency The acute form of this disorder may be the result of toxic damage to the cellular structure of the liver The treatment of this condition is discussed under the general heading of acute liver failure The management of acute infectious as well as homologous serum hepatitis, with or without associated jaundice, consists mainly of bed rest and supportive measures Experiments using lipotropic agents (choline and methionine) as well as intravenous injection of liver extract, have not significantly influenced the course of the

specific medication in addition to the regimen outlined above. Best results are obtained through administration of emetine hydrochloride, 0.065 gm intramuscularly daily for 12 days, in conjunction with carbarsone (Lilly), 0.2 mg twice daily for 10 days. This course may have to be repeated after an interval of 2 to 4 weeks.

Chronic Liver Insufficiency. Sufficient experimental and clinical evidence has been accumulated to prove that the life expectancy of patients with cirrhosis of the liver can be markedly increased through an appropriate dietary regimen (Patek and Post, Morrison). A diet of approximately 3600 calories has been advocated, distributed in the following manner: 139 gm of protein including the protein contained in brewers' yeast, 175 gm of fats, and 365 gm of carbohydrates. The main components of this diet are meat, milk, eggs, fruit, and green vegetables. Two generous servings of meat are prescribed, as well as 5 glasses of milk daily, three times with meals and twice in combination with 25 gm of brewers' yeast. As some patients will not tolerate yeast, capsules of vitamin B complex are substituted. Whenever the blood albumin level is low, parenteral as well as oral administration of amino acids is indicated. Intravenous medication using gelatin and albumin is advocated, even though this measure apparently fails to produce any significant alteration of the serum albumin level.

In the presence of ascites, fluids should be limited to 2000 cc, and the salt intake restricted to the extent of eliminating the salt shaker from the tray. It is, however, well to remember that with each abdominal tap which may become necessary in order to relieve circulatory embarrassment, an abundant amount of chlorides is incidentally removed. A too rigid restriction of salt is therefore, liable to precipitate hypochlor-

not prove successful in all cases. Routinely,

strated that these lipotropic agents contribute toward the establishment of a positive nitrogen balance. Crude liver extract administered either intravenously (intrahepatic—Lederle)—given daily in gradually increasing doses from 1 to 10 cc, diluted to 50 cc of 5 per cent glucose, or intramuscularly, has led to satisfactory results, although the manner of its action still remains obscure. Patek and Post suggest intramuscular injection of crude liver extract twice weekly. Other methods of treating ascites include medication with mercurial diuretics, especially a course combining mercuhydrin, 2 cc, or salyrgan, 1 to 2 cc, both intravenously once weekly or, if necessary, more frequently, with daily administration of ammonium chloride, 3 to 4 gm. Abdominal paracentesis may, of course, also become necessary (Barker).

Subcutaneous injection of ergotamine tartrate has been found to relieve pruritus in a certain number of cases (Lichtman). If this measure should fail to bring relief, procaine administered intravenously (20 cc of a 0.1 solution in 1000 cc of an isotonic solution of sodium chloride) holds reasonable hope of success. For the control of bleeding as well as of ascites, surgical procedures, such as the injection of sclerosing agents into the esophageal varices under esophagoscopy, and ligation of the left gastric vein, have been suggested (Moersch, Patterson and Rouse). Operative anastomosis between the splenic and the renal vein, to shunt a considerable volume of blood away from the portal system, will in some patients relieve portal hypertension, and decrease ascites (Blake more). Of late, endocrine substances, especially testosterone propionate, have been advocated for their ability to cause nitrogen retention in some instances, but to the present time only insufficient evidence as to their beneficial effect has been accumulated.

LUDWIG T. ROSENTHAL
LESTER M. MORRISON

REFERENCES

come necessary, although recent studies have demonstrated that even this measure may

Barker, W. H. Modern Treatment of Cirrhosis of Liver. *South Med & Surg*, 109:325, 1947.

Lakemore A H Portacaval Anastomosis for the Relief of Portal Hypertension *Gastroenterology* 11 488 1948

Correspondence Clinical Experience with Ergotamine Tartrate *JAMA* 107 148 1936

Duncan, G G et al Evaluation of Immune Serum Globulin as Prophylactic Agent against Homologous Serum Hepatitis *Am J M Sc* 213 53 1947

Javens W J Jr Infectious Hepatitis *Medicine* 27 243 1947

Joagland C L et al Analysis of Effect of Fat in Diet on Recovery in Infectious Hepatitis *Am J Pub Health* 36 1287 1946

Kunsell L W et al Protein Balance Studies in Patients with Liver Damage Role of Lipotropic Agents *Ann Int Med* 29 881 1948

Moersch H J Treatment of Esophageal Varices by Injection of Sclerosing Solution *J Thoracic Surg* 10 300 1941

Morrison L M Response of Cirrhosis of Liver to Intensive Combined Therapy *Ann Int Med* 24 465 1946

Patek A J Jr and Post J Treatment of Cirrhosis of Liver by Nutritious Diet and Supplements Rich in Vitamin B Complex *J Clin Investigation* 20 481 1941

Patterson C O and Rouse M O Sclerosing Therapy of Esophageal Varices *Gastroenterology* 9 391 1947

Rosenthal L T Diagnosis and Management of Obstructive Jaundice *Ann West Med & Surg* 1 124 1947

stores in the liver There is evidence that a liver generously supplied with carbohydrate food and able to store glycogen is less easily damaged by toxic agents than the glycogen depleted liver The carbohydrate may be

administration of glucose solutions becomes essential Hypertonic solutions of glucose may be used particularly in edematous patients since they promote diuresis and give a considerable caloric intake in small volume Fifty cubic centimeters of 50 per cent solution 200 cc of 25 per cent solution or 1000 cc of 10 per cent solution may be given at one time intravenously and repeated at intervals Where edema is not a problem 1000 cc of 5 per cent glucose may be given either intravenously or subcutaneously

ago by Peyton Rous For this reason an adequate protein intake or the administration of choline or inositol should accompany any pro-

PREOPERATIVE PREPARATION OF THE JAUNDICED PATIENT

The patient suffering from jaundice of hepatic origin when being prepared for surgery presents a number of important therapeutic problems which must be solved to the best of our ability to minimize the risks of operation Impaired hepatic function must be evaluated restored as far as is practicable and the liver protected against further injury Anemia if present should be adequately treated and thought should be given

possible

The liver parenchyma of the jaundiced patient suffers injury from biliary obstruction infection and various nutritional disturbances and will be subjected to the toxic effects of anesthetic agents and the traumatic insults of surgery in the operative period

Protective measures available include among others the restoration of glycogen

diabetes mellitus will usually require the use of insulin in the preoperative preparation of any jaundiced diabetic patient Regular insulin may be added to parenteral glucose solutions in the amount of 1 unit to each 2 or 3 gm of glucose This is usually advisable in the diabetic patient receiving glucose infusions and may also be of some value in nondiabetic patients in the preoperative period

Another protective measure for the jaundiced patient being prepared for operation is the provision of an adequate intake of protein The rate of depletion of liver glycogen in the fasting animal is less rapid if a generous protein intake was given previously The amino acid methionine present to the extent of about 3 per cent in most of our common food proteins protects against the development of fatty liver Many of our protein foods also contain some choline another protection against the fatty liver Protein is necessary for building hemoglobin for the manufacture of blood cells and for

the production of the plasma proteins and the replenishment of the protein stores of all the body tissues. Depleted plasma albumin often an accompaniment of severe liver damage may render the jaundiced patient more susceptible to pulmonary edema and to shock in the postoperative period.

tolerated it is often feasible to insure an ample intake of protein in liquid form. Suggestions for both solid and liquid diets for jaundiced patients will be given later in this article.

If adequate oral feeding is not possible we must resort to parenteral administration of blood and its products or amino acids. Transfusions of 500 to 1000 cc of whole blood or of 1 to 3 units of plasma or plasma albumin may be given daily or more frequently when speed is essential in preparing the patient for operation. Various preparations of amino acids such as amigen may be given as 50 gm dissolved in 1000 cc of 5 per cent glucose or normal saline and administered slowly intravenously. Rapid administration may give unpleasant reactions. Our aim should be to raise plasma albumin above 3 gm per cent in the patient's blood stream and total proteins above 60 gm per cent.

Periods of protein starvation caused by anorexia and vomiting, alcoholism and various types of chemical injury including chloroform anesthesia lead to the production of fatty infiltration of the liver. The value of a high protein diet in treating this condition has already been mentioned. Some restriction of fat intake to 1 gm per kilogram of body weight per day or less is probably advisable. The caloric needs are met by increase in the dietary carbohydrate. Other valuable aids in the prevention and treatment of fatty liver are the lipotropic agents *choline* and *inositol*. Both show little evidence of toxicity in the dosages here recommended.

Choline chloride and choline bicarbonate being deliquescent are best given as liquid preparations with various flavoring syrups (e.g., syrup of orange with the chloride) in doses of from 1 to 6 gm daily. Choline dihydrogen citrate is available in tablet form (0.6 gm each). One or 2 tablets may be

or dihydrogen citrate will usually overcome any tendency to gastric distress.

Inositol in my experience causes no gastric distress. It has been administered either in capsules containing 0.3 to 0.5 gm or in powdered form mixed with food. The dosage given has been 1 to 3 gm daily.

Anemia is frequently found in hepatic disease. It may be due to faulty storage of the antianemic factor of liver in the damaged organ. Protein starvation, recent hemorrhage or an associated splenic abnormality may also contribute to its causation. Treatment depends on the underlying cause. Liver extract should be administered orally (e.g., as Ixtron, 2 capsules three times daily) or parenterally in a dosage of 1 to 5 units hypodermically daily if the anemia is of the macrocytic type. Ferrous sulfate in a dose of 0.2 gm three times daily is indicated in hypochromic types of anemia. If the period of preoperative preparation must be brief it will be necessary to resort to blood transfusion. The erythrocyte count should be raised by these methods above 4,000,000 and the hemoglobin above 12 gm per 100 cc prior to operation if possible.

Protection against shock is afforded by restoration to normal of the plasma proteins and the cure of anemia by establishing fluid balance and attention to nutritional needs for minerals.

Protection against hemorrhage in the postoperative period requires the correction of any defects in the clotting mechanism and the capillary walls noted during the preoperative study of bleeding time, clotting time, prothrombin time, platelet count and capillary fragility. Of these the jaundiced patient is most likely to have a low level of blood prothrombin. The reason for this is that the exclusion of the bile salts from the intestinal tract which commonly occurs in obstructive jaundice brings about faulty absorption of vitamin K. In severe liver injury this organ may be unable to utilize vitamin K in the production of prothrombin even though the vitamin is available in adequate amounts. Discovery of a low prothrombin

blood level indicated by a prolonged prothrombin time calls for the administration of some form of vitamin K. Synkamin may be given orally in a dosage of 40 mg three times daily. Either synkamin or menadione may be given in similar dosages by hypodermic or intramuscular injection. If the low prothrombin is due to faulty absorption these preparations usually produce prompt improvement. If impaired hepatic function is the cause they may be ineffective. Prothrombin in such cases may be temporarily supplied by blood transfusion.

Cases with evidence of increased capillary fragility should be given rutin orally in a dosage of 20 to 40 mg three times daily. Vitamin C should also be given in a dose of 100 mg twice daily either by mouth or by parenteral injection.

Thrombocytopenia is treated by rutin and by transfusion of blood but if severe and persistent may call for consideration of splenectomy.

The diet of the jaundiced patient in the preoperative period should be planned with the following considerations. The caloric intake should be high in the patient of subnormal weight averaging at least 35 calories per kilogram of body weight using the patient's normal body weight as the basis of calculation. In the patient of normal weight caloric intake may be held at 25 to 30 calories per kilogram and in the obese patient should be reduced to 18 to 20 calories per kilogram again using the ideal weight of the patient as the basis of calculation.

Protein intake should be relatively high averaging 125 to 15 gm per kilogram of ideal weight. In those who are underweight or normal in weight fat is held to a level of about 10 gm per kilogram of normal weight. The remainder of the caloric allowance is made up by carbohydrate and will usually average 4 to 8 gm per kilogram of

carbohydrate intake in the last few days prior to operation.

If the patient is unable to eat solid food it is entirely feasible to prepare a palatable high protein liquid diet which will meet the above requirements. The following formula has been prepared and used successfully by the Department of Dietetics of the St. Mary's Group of Hospitals of St. Louis University.

Liquid Diet Whole milk 1000 cc dry skim milk 120 gm eggs 3 100 gm egg yolks 3 60 gm sucrose 80 gm lactose 40 gm dextrtomaltose No. 2 20 gm vanilla extract 150 cc water to make 1200 cc. Add to this thiamine 10 mg niacinamide 120 mg ascorbic acid 100 mg and ferrous sulfate 120 mg.

This supplies about 2050 calories protein 100 gm fat 70 gm and carbohydrate 250 gm. To reduce fat further the egg yolks may be omitted and the caloric loss made up by additional lactose and dextrtomaltose.

Occurrence of cheilosis, glossitis, neuritis, pellagra, skin lesions, and spider web venules calls for the administration of larger doses of the vitamins of the B complex than are described above given as tablets of fortified yeast 3 to 8 daily or parenteral injections of solutions of the mixed vitamins A, fortified fish liver oil containing vitamin A 10,000 units and vitamin D 1000 units is an additional desirable dietary supplement.

Parenteral infusions of isotonic solutions of sodium chloride or sodium lactate are of value in supplying fluids to dehydrated patients. They are essential in restoring the body's stores of sodium where these have been depleted by diarrhea, excessive sweating, or adrenal insufficiency. Calcium gluconate 1 gm three times daily in tablet form or by intramuscular or intravenous injection should be given if the blood calcium is low.

Antibiotics of appropriate type should be employed to control any actual infection found. Administration of penicillin 300,000 units in a slowly absorbable form may be begun as a prophylactic injection before operation and continued into the postoperative period. When the cost reaches lower levels aureomycin also may be used as a prophylactic against infection.

GORDON W. O. BROWN

allowance is made up by carbohydrate. Reducing diets are of value only if the surgical condition permits a preoperative period of sufficient length to allow weight reduction to occur. Cases that have been subjected to a reducing diet should have a more generous

REFERENCES

- Brown G O Treatment of Hepatic Cirrhosis *Post graduate Med* 4203 1948
 Brown G O and Muether R O Treatment of Hepatic Cirrhosis with Choline Chloride and D L Low in Fat and Cholesterol *JAMA* 118 1403 1947
 Direct observation on experiment carried out at the Rockefeller Institute in 1921

ACUTE CHOLECYSTITIS

The occurrence of an acute infection of the gallbladder presents the surgeon and the internist with a problem of considerable difficulty and one which requires careful judgment in its solution. Mild catarrhal cholecystitis may quickly subside spontaneously or the inflamed organ may be removed surgically without too great difficulty. The more severe forms of infection purulent and gangrenous cholecystitis have much more serious aspects. The surgeon often hesitates to operate while the inflammation is acute because the involved tissues of the gallbladder wall are in many instances so friable as to render removal difficult. Simple drainage which ordinarily can be carried out even in these circumstances without undue risk leaves behind a pathologic gallbladder which is likely to be the future site of the formation of calculi. Hence a delay in surgical inter-

infection into the peritoneal cavity. If the cystic duct is patent while the common duct is obstructed bile also may escape into the abdominal cavity a condition which greatly increases the gravity of the prognosis.

The patient suffering usually from severe pain in the right upper abdominal quadrant with associated anorexia, nausea and vomiting must be nursed carefully through the period of the acute infection, weighing carefully the symptoms and physical signs from day to day to decide the proper time for operation. Meanwhile the liver must be protected as well as possible from functional impairment so as to render the surgical procedure as safe as possible when it becomes necessary or desirable. The nursing staff as well as the attending physician should be

alert to recognize any unfavorable changes in the patient's condition.

The general care of the case of acute cholecystitis involves many of the principles discussed in the Preoperative Preparation of the Jaundiced Patient. In the early acute stages the patient as a rule will tolerate but little food. Parenteral administration of fluids to prevent dehydration often is necessary in this period. Glucose, 5 per cent solution in distilled water or isotonic sodium chloride solution may be used. However the necessity of maintaining nitrogen balance and preventing protein starvation is even more urgent in the presence of an acute infection than in the case of uninfected biliary obstruction. For this reason blood plasma or amino acid solutions should soon be added in any case unable to tolerate oral ingestion of proteins. The high protein liquid diet described in the preceding section should be given as soon as it can be tolerated, later gradually introducing more solid food. Fat causes gallbladder contraction and should be avoided.

If the patient is anemic transfusions of whole blood should be administered and liver extract 5 units daily given by hypodermic injection. As soon as nausea is present iron in the form of ferrous sulfate 0.2 gm three times daily should be prescribed.

The prothrombin content of the blood should be determined and if a deficiency is found vitamin K in the form of synkamin or menadione is to be given orally or parenterally in a dosage of 4 mg three times daily.

Fatty liver is to be avoided by use of a high protein, high carbohydrate and low fat diet and by the administration of choline and inositol. Choline may be given as the dihydrogen citrate one 0.6 gm tablet three times daily after meals with amphojel 15 cc. Inositol in a dosage of 3 gm daily may be given as a powder mixed with food.

Besides the maintenance of nutritional status the treatment of acute cholecystitis also includes measures to combat the existing infection. If this can be accomplished promptly it lessens the danger of rupture of the inflamed gallbladder and will hasten the return of the tissues to a more healthy state.

The patient should be kept at rest in bed but with frequent change of position from

or demerol (0.1 gm) by hypodermic injection

The introduction of the antibiotics has supplied the physician with measures which reduce the risks of this type of infection. There still remains, however, the problem of securing sufficient penetration of a sac-like structure such as the gallbladder by the antibacterial agent. Also the type of organism causing a given infection of the gallbladder is usually difficult to determine. This renders the choice of the most effective antibiotic uncertain. The most common in-

penicillin. However, the gram positive pyogenic cocci, streptococci, pneumococci, and staphylococci may occasionally infect the gallbladder. In these cases penicillin may be quite effective.

If it is decided to use sulfa drugs a combination of equal parts of the three sulfa

one alone. The fluid intake should be maintained at a level of at least 3000 cc per day. Sufficient alkali to insure alkalinization of the urine is desirable to reduce further the risk of crystal formation in the kidneys. Blood counts should be done daily to note any suggestion of toxic effect on the blood-forming organs such as agranulocytosis or hemolytic anemia. An initial dose of 4 gm should be followed by 1 gm every 4 hours.

Penicillin may be administered in aqueous solution in a dosage of 40,000 to 50,000 units every 4 hours or as procaine penicillin in aqueous or oily menstruum as an intramuscular injection of 300,000 units once or twice daily.

Streptomycin is more likely to be of value in infections due to gram-negative bacilli. This antibiotic must be given with some caution because of possible allergic reactions and toxic effect on the eighth nerve

and labyrinth in the form of impaired hear-

fewer allergic reactions. The dosage of both streptomycin preparations is usually from 1 to 2 gm daily. The daily dose is divided into three or four equal parts and given at 8 or 12 hour intervals. If any vestibular symptoms or impairment of hearing appear the drug should be discontinued.

Aureomycin offers some promise as an agent which should be effective against many of the types of infection which involve the gallbladder. It is administered orally in dosages of from 50 to 500 mg per kilogram of body weight per day. It is given at 4-hour intervals for the first 24 hours and then every 6

its use

These agents must be watched closely for their effect on the patient's symptoms and physical findings as well as the changes in fever, leukocyte count and sedimentation rate. By this means a decision is reached regarding the progress or suppression of the infection. If the infection is successfully overcome, operation is usually postponed for a period of several weeks. All of the precautions described in the preoperative care of the jaundiced patient should be exercised during this waiting period. Should it be decided that operation will not be done, even after the infection has subsided, the treatment then becomes that which will be described under the section on Chronic Noncalculous Cholecystitis.

GORDON W. O. BROWN

CHRONIC NONCALCULOUS CHOLECYSTITIS

The problem of chronic noncalculous cholecystitis differs from that of acute cholecystitis because the infectious process is usually mild and presents little danger of rupture and peritonitis. The chief complication likely to arise is the formation of calculi. To this must be added the possibility that chronic irritation may favor the occurrence of neoplastic changes with resultant cancer of the gallbladder or bile ducts. The chronic

recurrent inflammation reactions --
cause ann
and more

The symptomatology includes repeated attacks of pain in the right upper abdominal quadrant with aggravation of symptoms after ingestion of fatty foods. During cholecystography failure of visualization, poor concentrating power, and failure to empty after a fat meal are suggestive evidences of the existence of chronic cholecystitis. Calculi cannot be dissolved by medicinal treatment.

trial of medical care can legitimately be attempted

The principles underlying the medical measures usually suggested are promotion of increased flow of bile, relaxation of the sphincter of Oddi, and stimulation of gall bladder contraction. In the alternate filling and emptying of the gallbladder, the hope is that drainage of inflammatory products will be promoted, the bile ducts cleared of debris, and any small precipitates that might be future nuclei of stones flushed out from the organ.

It is probably unwise to make use of this form of treatment during any period in which acute symptoms are present. The treatment of such a period should follow closely the suggestions given for the treatment of acute cholecystitis, particularly rest in bed, relief of pain by sedation or opiates if necessary, low fat diet and use of antibiotics if active infection appears to be present. When acute symptoms have subsided, it then becomes feasible to attempt to clear the biliary tract and attempt to restore the gallbladder to normal function.

Administration of preparations of bile salts is among the most effective methods of in-

creasing the fluid output of bile. Preparations such as bilron, ketochol, or decholin in a dosage of 0.25 gm three times daily after meals may be given. Since the discovery of Meltzer and Auer that magnesium sulfate causes relaxation of the sphincter of Oddi and contraction of the gallbladder, the use of saline cathartics in the treatment of chronic cholecystitis has had some justification. Magnesium sulfate (60 cc of 33 per cent solution) may be given orally in a glass of water or may be given directly into the duodenum through a duodenal tube. Sodium sulfate or sodium phosphate (4 gm) may also be given. Perhaps the most palatable preparation is the effervescent solution of magnesium citrate (200 to 350 cc). The line laxatives are best given in the morning before breakfast.

Spasm of the sphincter of Oddi may be a complicating factor in cholecystitis. Nitroglycerin (0.0006 gm), sodium nitrite (0.00 gm) and theophylline ethylene diamine (0.1 gm) are substances believed to have the ability to relieve spasm. They may be given three times daily after meals with bile salts.

Fat is one of the most powerful agents

infection is acute but in the stage where

of these substances may be given three times daily before meals. One reason for caution in the use of fats even in quiescent stages of cholecystitis is the belief that high fat diet favors the formation of biliary calculi. However, if coupled with bile salt administration there is probably not too much danger of calculus formation.

GORDON W. O. BROWN

DISEASES OF THE PANCREAS

ACUTE PANCREATITIS

Acute pancreatitis implies an acute inflammation resulting from the action of pancreatic enzymes within the injured ducts of the pancreas. The varying types of acute pancreatitis were classified by Pratt as fol-

lows: (1) acute pancreatic edema, (2) acute pancreatic necrosis with or without hemorrhage, and (3) suppurative pancreatitis (abscess of pancreas). Many other students have accepted his classification.

After the acute episode has passed, the patient should be carefully observed to de-

etermine the etiology Rich and Duff believe that the majority of cases of hemorrhagic pancreatitis result from partial obstruction of the small ducts owing to metaplasia of the ductal epithelium resulting in rupture of the small ducts The freed pancreatic ferments by their digestive action destroy local arteries and veins and hemorrhage occurs If no blood vessels are affected the local tissue becomes edematous This theory

edema of the pancreas acute hemorrhagic pancreatitis and acute pancreatic necrosis The role played by the biliary tract in the average case is questionable and in view of the above concept is rarely a prime etiologic factor This concept permits a much different approach to the management of acute pancreatitis from that in vogue in the early decades of this century

Experience however cannot fail to impress one with the high coincidence of gall bladder disease with acute pancreatitis and the fact that there is a relationship between the two has long been recognized Sixty per cent of cases of acute pancreatitis are accompanied by biliary tract disease and it may be further assumed that a certain percentage will be associated with common duct obstruction from stone in the ampulla of Vater or reflex from spasm of the sphincter of Oddi The action of enzymes on the tissues in the presence of an obstruction of the pancreatic biliary tract system may account for the acute disturbance

Acute pancreatic hemorrhage and necrosis have also been shown to be caused by obstruction of the pancreatic ducts occlusion

Too frequently acute pancreatitis is confused with primary acute biliary tract disease It must also be differentiated from coronary occlusion perforating peptic ulcer intestinal obstruction and renal calculus Routine performance of serum amylase tests in all cases of acute abdominal disorders greatly increases the accuracy of diagnosis This of course is of the greatest importance since it is now almost universally agreed

that acute pancreatitis should be treated conservatively

Active Treatment As previously indicated the pathologic process varies with the particular circumstance in the pancreas Acute edema or even mild hemorrhage may subside within a few days without any major complication A large hemorrhagic process may be followed by local necrosis Any of these may resolve satisfactorily without the necessity of any surgical interference On the other hand when the process is extensive and followed by shock and vasomotor collapse the problem is one of an acute emergency and demands every aid Some of these patients may die within a few hours of onset These individuals should not be operated on since in this state of collapse surgery will most certainly be fatal A much lower mortality is maintained in such severe cases with the ultraconservative program Perhaps the most difficult decision to make is the decision not to operate when the patient is so ill with an intra abdominal catastrophe

As soon as the diagnosis of acute pancreatitis is made certain supportive measures must be instituted The general management is directed toward the present symptoms In mild attacks hot fomentations should be applied to the epigastric area and continued constantly An enema of warm physiologic saline often brings relief of the distention and discomfort

When the attack is severe pain and moderate shock must be dealt with Morphine sulfate $\frac{1}{2}$ grain (15 mg) is given and repeated in one hour if necessary for pain

atropine
mouth
strolling
pain and less likely than morphine to cause sphincter contraction If morphine is given atropine sulfate $\frac{1}{100}$ gram (0.6 mg) should be combined with the first dose to control pylorospasm and other sphincter contraction Relief from pain may also be obtained by slowly injecting intravenously 10 cc of a sterile 10 per cent solution of calcium gluconate This may be further justified since it is reported that there is a decrease in blood calcium values in acute pancreatic necrosis Papaverine and atropine are both effective in diminishing secretions of the

pancreas and relaxing the sphincter of Oddi.

Nausea, vomiting, and dehydration, which so often accompany the severe attack, result in disturbances to the general body chemistry. In order to evaluate properly the electrolyte and serum protein balance the following studies should be immediately undertaken: blood count and blood typing, blood chemistry studies to include serum proteins, pancreatic ferments, chlorides, calcium, and CO₂ combining power.

The severe attack should be combated by intravenous administration of 1000 cc of 10 per cent glucose in normal saline solution. When the blood volume and cells have fallen or the serum proteins are at a critical level, 500 cc of whole blood or plasma should be given as a transfusion and repeated every 24 to 48 hours until the critical stage has passed and the blood levels return to a reasonably normal status.

Gastric dilatation and ileus are best controlled by Wangenstein continuous suction or by introduction of the Muller-Abbott tube.

Inasmuch as infection plays a part in some cases, penicillin 50 000 units intramuscularly every 3 hours, and sulfonamides intravenously or by mouth may be given until the bacterial invasion is under control.

Ascorbic acid, 500 mg, and injectable vitamin B complex, both given intravenously once daily, may aid in more rapid convalescence. In the presence of jaundice, vita-

ferments in the pancreas. Magnesium sulfate, 30 cc to 60 cc of 30 per cent solution by nasal tube four times daily for several days, facilitates biliary flow into the duodenum.

Since all foods must be withheld for several days it may be necessary to supply

fat. The usual hydrolysates are recommended because of ease of digestion.

If constipation is present, 1 or 2 drams sodium phosphate in a glass of hot water before breakfast is indicated to aid biliary function and drainage of bile and pancreatic secretions into the duodenum.

A small single dose of roentgen rays appears to inhibit amylase enzyme production and minimize the degree of pancreatic tissue destruction.

A practice worth following is to operate only when there is reasonable doubt of the diagnosis or when it becomes evident that the patient is not improving.

to investigate further the cause of pancreatitis. One may be reasonably safe with diagnosis if a careful study is made of onset and progress of the case, and if the result of the serum amylase test is available. If there is reasonable doubt in the diagnosis the patient should not be refused the benefit of abdominal exploration, and if the diagnosis of acute pancreatitis is found the minimum of surgery should be undertaken and the pancreas left alone. When evidence of local necrosis or abscess is present and surgery is deemed imperative, the measure must be instituted to raise the patient's health status to permit surgery. Proper drainage of the necrotic process then be undertaken.

In the presence of gallstones or persistent jaundice, operation should be performed when the patient seems to have reached maximum of recovery. Duodenal drainage by Lyon's method has been instituted with undetermined but suspected biliary disease has been considered. Because of the relatively high incidence of biliary tract disease in acute pancreatitis, there is a reason to remove all gallstones as a prophylactic measure.

LOWELL D. S. O.

CHRONIC PANCREATITIS

At first such foods as thoroughly cooked strained cereal, rice, and fruit juice may be tried in small amounts at frequent intervals. If these foods are well tolerated, it is desirable to return to a general diet consisting of high carbohydrate, low protein, and low

Chronic pancreatitis results from a previous episode or repeated episodes of inflammatory process, from degenerative changes in the pancreas from syphilis, chronic nephritis, or arteriosclerosis, or from inflammation from contiguous organs.

■ disorder observed clinically with relative infrequency

The symptoms are often confused with those of disorders of the intestine or of gall bladder infection. Chronic pancreatitis usually reveals itself by attacks of distress discomfort, or pain in varying intensity in the epigastric region, and the presence of large, bulky, fatty malodorous gray stools. The stools when examined reveal fatty acid crystals and soaps and at times undigested muscle fibers.

In the advanced state marked disturbances in nutrition are observed. Jaundice is sometimes seen and glycosuria ■ occasionally present. Roentgen studies may disclose pancreatic calculi.

Active Treatment The general management of chronic pancreatitis is dependent on the many factors which must be considered causative. Since the symptoms are often associated with biliary tract disease or disease of adjacent structures which has contributed to the inflammation of the pancreas, these conditions must also be considered in treatment. Conservatism is the policy, although no hard and fast rule can be made or adhered to.

Pancreatic insufficiency occurring after marked destruction of the pancreas, either in acute pancreatitis or in the more slowly de-

tapioca, cottage cheese, rice, well cooked farina, cream of wheat, corn meal mush, strained oatmeal, and melba toast are included in the diet. Citrus fruit juices and strained cooked fruits may be taken in small amounts. All fluids should be given warm. Hydrolyzed proteins and protein milk, although low in calories, promptly satisfy the protein starvation.

The total caloric content ■ insufficient on the above foods unless the patient ■ fed every 2 to 3 hours.

Achlorhydria is a common finding and when present requires dilute hydrochloric acid. It may be given in 10 to 20 minims three times daily before meals, in $\frac{1}{2}$ glass (100 cc) water.

Pancreatic extract U.S.P., 10 grains, (150 mg.), preferably in enteric coated tablets, before or with meals three times daily, is essential. Raw ground pancreas, although difficult to take, has been fed to patients with good results.

Tincture of belladonna, 10 drops, or extract of belladonna, $\frac{1}{2}$ grain (15 mg.), three times daily after meals may be given for intestinal unrest.

Calcium carbonate 15 grains (1 gm.), three times a day, half an hour before meals is useful because it binds the free fatty acids, powdered extract of opium $\frac{1}{2}$ or 1 grain (30 to 60 mg.), three to four times daily, or tincture of opium U.S.P., 5 to 10 drops four times daily, may be given to control the diarrhea.

Since one of the major complications in chronic pancreatitis ■ disturbance in nutrition the following are recommended: liver extract (15 units 1 cc intramuscularly, once or twice weekly), folic acid, brewers' yeast tablets or yeast extract, vitamin B complex, injectable 1 cc intramuscularly or synthetic preparation for intravenous administration, ascorbic acid 500 mg intravenously once daily. Many of these may be given less often as the nutritional status improves, but should be continued indefinitely as indicated.

The stools should be studied and carefully followed to observe the effect of treatment.

Moderate to strict dietary supervision is followed by gratifying results. Nutrition is improved and the stools may return to a fairly normal state, although remissions are frequently observed after dietary indiscre-

restriction is the rule.

Diet ■ in most cases the important aspect of treatment. Diet may or may not be severely restricted, depending on the evidence in the stools of inadequate digestion of fats, protein, and carbohydrates. As a rule, more than one ferment ■ deficient but digestion of fats is particularly disturbed. At first a fat free diet should be planned avoiding roughage and high cellulose foods. Steatorrhea is usually promptly controlled, although it is not necessary that fat disappear completely from the stools since ■ little fat ■ usually without irritating effect. The undigested fatty acids increase acidity in the intestine, which results in secondary diarrhea. Usually skimmed milk, gelatin, finely ground lean meats, soft boiled egg, hydrolyzed milk proteins, vegetable purées,

tions or following mild exacerbations of subacute attacks of pancreatitis. One patient, observed over a period of twenty years, is maintained today on a moderately restricted diet and an adequate amount of pancreatic extract. Another patient, who recently died at the age of 82, was known to have shown signs of chronic pancreatitis for more than 20 years, and in his latter years developed diabetes and had numerous calculi in the pancreas but remained in a state of good nutrition with only moderate dietary restriction.

Experience justifies the conservative, non-surgical procedure. Rarely is the problem of pain so severe as to require operation, although no patient should be denied radical surgery when other measures for the control of pain fail. The presence of pancreatic calculi is not an indication for operation unless pain and obstructive symptoms make it imperative. The relative frequency of the finding of pancreatic calculi by roentgen studies in patients with few symptoms would seem to preclude the need for their removal as a routine procedure.

Biliary tract disease, gallstones, obstructive jaundice, and chronic perforating peptic ulcer, or suspected pancreatic carcinoma should all be dealt with by proper surgical measures.

LOWELL D. SNORF

REFERENCES

- Comfort M W, Gambill E E and Baggenstoss A H. Chronic Relapsing Pancreatitis. Study of 29 Cases Without Associated Disease of Biliary or Gastrointestinal Tract. *Gastroenterology* 6:239 876 1948
- Popper, H L. Acute Pancreatitis. Evaluation of Classification, Symptomatology, Diagnosis and Therapy. *Am J Digest Dis*, 15:1 1948
- Rich A R, and Duff C L. Experimental and Pathological Studies on the Pathogenesis of Acute Haemorrhagic Pancreatitis. *Bull Johns Hopkins Hosp* 58:212 1936

CELIAC SYNDROME

The term "celiac syndrome" includes several clinical varieties of a disorder in which the essential feature is a defect in fat absorption. Celiac or Gee Herter-Heubner disease in early childhood has its counterpart as sprue in adult life. Each disorder has as its major sign idiopathic steatorrhea or fatty diarrhea. The stools contain large amounts of fat in the form of fatty acids and soaps,

and these cause intestinal irritation and diarrhea. Carbohydrates are sometimes poorly handled, although this failure is not the result of a defect in absorption but of a disturbance in intestinal function.

Sprue must be considered as a deficiency disorder superimposed upon an already defective organism disturbed by infection.

between celiac disease and sprue is the age of the patient affected.

Active Treatment. Since the etiology of celiac disease and sprue is unknown treatment must be directed to avoidance of precipitating factors, to symptomatic management of defects in fat and carbohydrate digestion, to specific management of acute crises, and to control of secondary disturbances related to nutritional deficiencies. Treatment is similar in both adults and children, the major difference being in amounts of medication and food given. Dietary and supplementary considerations are identical. In general, all other factors of management are subordinate to liver therapy and diet.

Acute gastroenteritis may precipitate an acute crisis at any age. Questionable foods and contact with contagious and infectious diseases should be avoided. When infectious disease is present, daily injections of penicillin, 300,000 units of the depot - 4 hours spiratory is indi-

cated

In the infant, child, or adult with celiac crisis, oral fluids are to be withheld and the fluid and electrolyte balance controlled by parenteral administration. Intramuscular liver extract, calcium gluconate, vitamin B complex, and vitamin C parenterally are given as early as possible and continued daily until the stomach and intestine are found tolerant to them and food. The specific dosage of these substances is discussed later.

From this point on and to control the chronic state, management by diet, liver extract, vitamins, and mineral supplements is of utmost importance. Emphasis is on a heavy protein diet, low in fat and restricted in carbohydrates. Foods should be easily assimilable and require minimal functional

efforts of the intestine. In children the diet at first should consist of protein milk amino acids or protein hydrolysates in broth or bouillon gelatin with fruit flavor weak tea and warm or hot water. Later the following may be added finely ground lean beef minced white meat of chicken cottage cheese puréed spinach, squash, celery green beans and asparagus tips.

If the stools tend to loosen after the above additions the quantity of vegetables should be reduced. As the stools continue to have a normal consistency more vegetables should be given and citrus fruits and cooked canned and puréed fruits such as pears, peaches and apricots may be added. Banana or banana powder has long been recognized as a well tolerated fruit.

There may now be a gradual transition to a fairly normal and adequate diet. Butter and whole milk should be added with the greatest caution. Milk is usually poorly tolerated a fact which suggests an allergy component and which demands further study. The stools should be regularly analyzed especially with the increase in fats to determine if these additional foods are being digested. Inasmuch as carbohydrates are at times poorly digested such starches as potato and rice are to be cautiously added and stools checked for starch granules. If there is increased fermentation in the stools carbohydrates must be reduced.

Since the prescribed diet provides a low caloric intake it is necessary to find the carbohydrates and fats best suited to the individual desires and tolerance and add them as rapidly as possible. Protein hydrolysates as protein supplement have been found to be of inestimable value.

The intestinal functional balance is often sensitive and may be upset by emotional disturbances and fatigue and too rapid additions to the diet. The patient should always be cautioned to eliminate foods to which he has previously found himself sensitive and this should be further emphasized if there is a history of allergy. Fats in the form of fried foods gravies and oily fish should be avoided and the quantity of all fats should be limited.

Recurrence of characteristic symptoms at any stage demands immediate modification of the diet.

Vitamins may be given as concentrated fish liver oil 5000 to 10000 international units daily provided it is tolerated. Ascorbic acid in citrus fruits and tomato juice, or 100 mg tablets two to three times daily should be administered. Brewers yeast powder folic acid or a liquid yeast extract or vitamin B complex will supply vitamin B.

Liver extract or vitamin B complex injectable is given two to three times weekly at first and usually 1 cc of liver extract is advised to be taken once a week parenterally for an indefinite period. Crude liver or the concentrated form is equally effective. The new vitamin B₁₂ 30 micrograms three times a week may prove to be more effective than liver extract.

Alcohol is harmful and must be avoided as should laxatives. Transfusion is rarely necessary.

Remission of intestinal symptoms and improvement in the nutritional status often occur with dramatic promptness. Proof of the adequacy of the regimen is noted first in the change in the character of the stools. They are less frequent, contain more color and less

The child or adult with celiac syndrome usually is faced with a long and discouraging trouble. The active phase with its outstanding symptom of defective fat absorption is followed by invalidism, anemia and mineral vitamin and protein deficiency unless early well chosen and prolonged therapy is instituted. Inadequate treatment leads to chronic invalidism and the disease may in fact result in death when not treated early or thoroughly enough.

The celiac syndrome must be considered a chronic disease and the patient requires constant strict supervision and control to avoid the recurrences so often precipitated by emotional bouts, intercurrent infections and sundry intestinal upsets.

LOWELL D. SNORR

REFERENCE

- Hanes F M and McBryde A. Identity of Sprue, Nontropical Sprue and Celiac Disease. *Arch Int Med* 58:1 1936.

DISEASES OF THE RESPIRATORY TRACT

DISEASES OF THE TRACHEA AND BRONCHI

ACUTE AND CHRONIC LARYNGITIS

As a rule laryngitis requires only symptomatic measures for treatment. The most specific remedy is voice rest. Most of the treatment is directed at the accompanying symptoms of the upper respiratory tract infection. A few days of bed rest are usually indicated and this should be in an atmosphere free of chemical and physical irritants such as noxious fumes and dusts. Smoking and the use of alcoholic beverages should be forbidden. The diet may consist of any food desired, but liquids and soft foods are usually more appetizing and better tolerated during the acute stage. Iced drinks and cold foods such as ice cream are soothing.

Local applications of warm or cold compresses may make the patient more comfortable. In the presence of nasal congestion, one of the various popular nose drop preparations may be prescribed for symptomatic relief. General malaise and fever usually can be controlled with 10 grains (0.65 gm) of acetylsalicylic acid. The use of codeine in $\frac{1}{4}$ (15 mg) or $\frac{1}{2}$ (30 mg) grain doses every 4 hours may be necessary to relieve more severe discomfort or annoying and irritating cough. One quarter (15 mg) or $\frac{1}{2}$ grain (30 mg) doses of phenobarbital, 10 (0.65 gm) or 15 grains (1 gm) of a satisfactory bromide or any other suitable sedative may be used to prevent restlessness. Larger doses are required to relieve insomnia.

and husky or the patient is able to speak only in a whisper, there should be a minimum of conversation and preferably none. Rest of

the vocal cords should be stressed above all else in the treatment of laryngitis. Steam inhalations produce soothing symptomatic relief. Compound tincture of benzoin, 1 tea spoonful to a pint of water, makes the inhalation more pleasant. The steam may be produced from an electric water vaporizer or from a simple steam kettle. Inhalations for periods of 20 minutes several times daily are frequently beneficial.

Antibiotic or sulfonamide preparations are rarely indicated. However, in the presence of debility, an overwhelming infection, or other significant complications, penicillin, streptomycin, other antibiotics, or a suitable sulfa drug, singly or in combination, may be indicated in full therapeutic doses. Penicillin and sulfa drug lozenges have small value in the treatment of even mild laryngitis. At times laryngitis may require the direct application of shrinking solutions or other therapeutic agents such as 0.5 per cent silver nitrate. Recourse to this procedure is rarely indicated since the simpler measures already discussed are usually effective. Antibiotics

frequently useful in inflammatory disease the larynx. A suitable antibiotic administered with benadryl is a satisfactory and effective combination (see section on Bronchitis and Bronchiectasis). With subsidence of the acute symptoms, the same precautions and treatment should be followed during the first few days of convalescence. If there is a recurrence of symptoms, the management is the same.

In chronic laryngitis the principles of treatment are generally similar but must be administered over a longer period of time. If laryngitis persists in spite of adequate ther-

aply the vocal cords should be visualized either with a mirror or even better by direct laryngoscopy This is done to rule out the possibility of laryngeal tumor tuberculosis syphilis or other serious disease entities Treatment in these instances is more specific but frequently futile In some cases of chronic laryngitis it becomes necessary to retrain the voice This is especially true of public speakers and singers with a history of recurrent and troublesome laryngitis

LOUIS L. FRIEDMAN
SANDY B. CARTER

ACUTE TRACHEOBRONCHITIS

bed a few days until the symptoms begin to clear In the presence of fever bed rest is mandatory In any event the infection will be more easily and quickly controlled if the patient remains in bed in a warm and well ventilated room free of chemical or physical irritants Smoking and dust are to be avoided Dietary restriction is unnecessary although during the acute stage a liquid or a soft diet will usually be more palatable Fluids are frequently forced and alkalis recommended However there is no proof that either of these measures is of any therapeutic value Steam inhalations should be prescribed for 20 minute intervals three or four times daily These can be administered from an electric water vaporizer or an ordinary steam kettle One teaspoonful of compound tincture of benzoin may be added to each pint of water to be vaporized This practice produces a pleasing aroma but actually the steam is primarily responsible for any resulting symptomatic improvement

Acute tracheobronchitis is usually accompanied by nasal congestion and drainage This annoying complication demands attention since the nasal discharge will gravitate into the trachea and bronchi and produce additional signs and symptoms Numerous proprietary sympathomimetic preparations are available for relief of the nasal symptoms We prefer privity hydrochloride A host of proprietary nasal drops with an added antibiotic or suitable sulfa drug are also available but the specific therapeutic benefits

claimed for these combining types of nose drops are probably exaggerated Three to 5 drops of privity hydrochloride in each nostril three or four times daily are usually sufficient to control the nasal symptoms No sympathomimetic nose drop should be prescribed in the presence of such acknowledged contraindications as hypertension hyperthyroidism or diabetes mellitus In these instances a satisfactory measure of relief can be obtained with warm saline irrigations Chloresium nasal drops produce satisfactory symptomatic relief and do not possess any of the undesirable sympathomimetic qualities At no time should the use of nose drops in an oily base or a nasal jelly be prescribed The danger of a complicating lipid pneumonia especially in the very young and the aged far exceeds the possible therapeutic benefits which may be expected from this practice Interference with ciliary activity is an added disadvantage The addition of an antihistaminic agent to any of the acceptable sympathomimetic nose drop preparations appears

cient to control general malaise If this is not effective $\frac{1}{4}$ (15 mg) or $\frac{1}{2}$ grain (30 mg) of codeine can be administered in addition. Relief of restlessness and insomnia may be accomplished with the use of adequate doses of a satisfactory barbiturate or bromide Cough may be the most annoying symptom in tracheobronchitis No treatment is needed for mild cough If the secretions are excessively thick and tenacious expectorants are required to combat useless cough and resulting discomfort Expectorants should be used only when specifically indicated Injudicious use of expectorant drugs may mask the clinical symptoms or actually cause spread of infection as a consequence of the increased production of watery bronchial secretions Profuse and tenacious bronchial secretions may cause respiratory embarrassment requiring the use of oxygen In the very young regardless of what remedial medical or surgical measures are used death frequently supervenes in serious cases Useless annoying and exhausting cough may require the use of an anodyne in suitable dosage The best way to control cough is with codeine in $\frac{1}{4}$ or $\frac{1}{2}$ grain (15 to 30 mg)

doses The codeine may be incorporated into a palatable cough syrup or administered in tablet form Cough must not be suppressed entirely because coughing is necessary to expel the accumulating bronchial secretions Complete suppression of cough or the use of belladonna derivatives is fraught with danger The retained or inspissated sputum may cause atelectasis

The use of sulfa drugs or antibiotics is rarely indicated In the presence of an overwhelming infection or debility, however, one or both of these remedial agents should be used in adequate dosage Systemic administration of chemotherapeutic or antibiotic agents frequently fails Troches as a rule have only psychic value Aerosol therapy is the best approach to the effective treatment of acute tracheobronchitis (A complete discussion of this form of therapy will be found in the section on Chronic Bronchitis and Bronchiectasis)

LOUIS L. FRIEDMAN
SANDY B. CARTER

CHRONIC BRONCHITIS AND BRONCHIECTASIS

The increased utilization of available chemotherapeutic or antibiotic agents and a better understanding of the pathologic physiology has improved the outlook for patients suffering from chronic bronchitis and bronchiectasis With proper use of the newer drugs, the results achieved in some instances are most encouraging Nevertheless, the treatment of bronchial conditions is still largely symptomatic Both of these diseases are generally secondary manifestations, or complications, of a multitude of local thoracic, distant, or systemic diseases Therefore, in order to prevent entirely, or to modify, the severity of chronic bronchitis and bronchiectasis energetic and expectant therapy of responsible primary diseases is essential In any event, correct identification of the primary disease is the prerequisite for the successful therapeutic management of these bronchial disorders when they develop

The clinical results achieved with systemic administration of various chemotherapeutic and antibiotic agents in cases of chronic bronchitis and bronchiectasis have been disappointing Appreciation of the pathologic

alteration of the bronchial mucosa and neighboring pulmonary tissue resulting from these conditions explains the usually equivocal, or actually unsatisfactory, results obtained when treatment is confined to the systemic route Specific and indicated symptomatic drugs administered by the various systemic routes in these instances are unable to penetrate the resulting pulmonary tissue barriers in sufficient quantities to establish effective therapeutic levels at the site of infection This shortcoming accounts for the failure of *in vivo* results with specific drugs to approach, or to parallel, their demonstrable antibacterial activity *in vitro* Topical, as well as systemic, therapy is indicated in order to achieve the expected clinical benefits Again, the results achieved following the use of various sulfa drug preparations by nebulization or direct bronchoscopic instillation have been discouraging The antibacterial activity of sulfa drugs is inhibited in the presence of purulent exudates Antibiotic agents on the other hand are effective when administered as aerosols

Aerosol Therapy Aerosol antibiotic therapy of chronic bronchitis and bronchiectasis may produce truly remarkable and unanticipated successes Aside from surgical removal of the involved pulmonary tissue in bronchiectasis, it is the most important and effective therapeutic measure in these bronchial disorders

The aerosol solution is delivered by means of a satisfactory nebulizer Many nebulizers and innumerable methods of administration have been devised The writers prefer the Vaponefron apparatus Although the apparatus and method of choice are a matter of individual preference, better results and better patient co operation can be obtained with the less complicated techniques Even with the simplest apparatus careful education of the patient as to proper breathing and the art of self administration is of primary importance As a general rule, we prefer not to exceed a volume of 2 cc or 2.5 cc of the solution to be nebulized at each treatment Larger amounts are apt to be tiring to the patient regardless of the method of administration Other investigators have reported satisfactory results with the use of aerosol penicillin prepared as a "dust," but in our experience liquid aerosol therapy is nevertheless prefer

tions of patients who are considered suitable candidates for aerosol therapy should be determined before treatment is instituted. This can be ascertained quickly by examining a Gram stain of a satisfactory sputum specimen microscopically. Although the exact nature of the offending microorganism or organisms may not be ascertained accurately by this method, it nevertheless serves to classify the responsible etiologic agent as gram negative or gram positive. This information is usually adequate and facilitates the rapid institution of effective therapeutic measures. The effect of aerosol therapy on the bronchial infection can then be followed by daily Gram stain examinations of the sputum. If the anticipated therapeutic response is not achieved, additional bacteriologic studies should be carried out in order to identify specifically the offending microorganism.

The nontuberculous pathogens responsible for bronchial infections are generally gram positive and will usually respond to aerosol penicillin therapy. Occasionally after the gram positive organism is eradicated the bacterial flora will undergo a relative and an absolute increase in both the variety and number of gram negative bacteria. Although these organisms are commonly considered to be nonpathogenic as secondary invaders, they are unquestionably responsible in many instances for a protracted period of disability

bacteria, it becomes necessary to supplement the treatment with streptomycin. These two antibiotics used in combination can generally handle all of the more common bronchial infections. When streptomycin and penicillin are used simultaneously, it is advisable not to use the calcium salt of penicillin with streptomycin sulfate since calcium sulfate is precipitated in this solution and will thus interfere with the mechanical efficiency of the nebulizer. The dosage of penicillin employed varies from 25 000 units to 50 000 units per cubic centimeter, and the dosage of streptomycin usually employed varies from

50 000 units (0.5 gm) to 100 000 units (1.0 gm) per cubic centimeter. Normal saline is used in preference to distilled water as a solvent for either of these or other antibiotic agents. It is the authors' opinion that normal saline is less irritating to the mucous membranes than distilled water. Some patients develop a sensitivity to penicillin or streptomycin or both. Unless the allergic manifestations are alarming, treatment is continued with the assistance of one of the antihistaminic drugs.

In the absence of any of the acknowledged contraindications, a suitable sympathomimetic agent should be added to the aerosol solution in order to relieve bronchial edema and spasm. Frequently, the disturbing clinical symptoms which accompany these pathologic changes in the bronchi either disappear completely or are markedly diminished. When edema and spasm are marked, the use of 0.5 cc to 1 cc of inhalation adrenalin (1:100) in the aerosol solution may be necessary to achieve the desired results. When sympathomimetic drugs are not indicated, one minim of 2 per cent tyrothricin solution per cubic centimeter of aerosol solution provides a safe and effective concentration. Tyrothricin usually prevents the rapid multiplication of gram negative bacteria and precludes the use of supplementary streptomycin. It is not only a valuable prophylactic measure clinically but also tends to preserve the patient's economy. The use of a satisfactory antihistaminic in the aerosol solution produces many of the desirable effects which result from the administration of sympathomimetic drugs.

biotic solutions and have observed that the incidence of local pulmonary and other allergic reactions is noticeably diminished. This advantage may justify the routine use

cubic centimeter) is effective. In addition to producing the desirable effects of the sympathomimetic drugs, it also acts as a satisfactory expectorant. Annoying, useless cough is accordingly converted to a productive non

exhausting cough. In cases of allergic bronchitis, the use of aerosol benadryl results in dramatic clinical improvement. Those cases which fail to respond to systemic administration of antihistaminics are benefited by aerosol administration. Varying concentrations of penicillin, tyrothricin, streptomycin, adrenalin and benadryl in the desired amounts may be administered in the same aerosol solution.

Aerosol antibiotic therapy should be continued until the maximal beneficial response has been achieved. The number of daily treatments and the dosage of the antibiotic agent depend on the nature and severity of the illness and should be adjusted frequently to parallel the clinical and laboratory response. The chest roentgenogram should not be used as a barometer of therapeutic response since it does not necessarily parallel the clinical progress of the disease. Initially, the more serious cases may require four daily treatments. In the presence of concomitant sinus infections which so frequently complicate the picture of chronic bronchitis and bronchiectasis, aerosol therapy by the nasal route should be carried on simultaneously. Both areas of infection must be controlled in order to obtain satisfactory results. Lingering infection in either area predisposes to infection of the other. The frequent association of sinusitis and chronic bronchitis has justified the existence of the descriptive term *bronchosinusitis*.

The intelligent use of aerosol antibiotic therapy in cases of chronic bronchitis due to infection will achieve not only striking palliative results but in many instances, lasting cures. Systemic antibiotic therapy is unnecessary and useless once the extrapulmonary manifestations of the primary disease are controlled. The therapeutic management of the case may then be confined to the aerosol route. Aerosol therapy does not cure bronchiectasis. It affords effective symptomatic relief and is additionally valuable in the preoperative preparation of these patients for surgical excision of the involved pulmonary tissue. Furthermore, many patients who, in the past, would have been denied the benefits of surgical therapy because of their debilitated condition, may now be converted into suitable candidates for surgery. Aerosol antibiotic therapy of

pseudobronchiectasis generally results in permanent cures.

Although this presentation primarily stresses the benefits of penicillin and streptomycin aerosol therapy, it is important to note that many other drugs can be prepared for use in this manner. As newer antibiotic agents are discovered and made available many of them will undoubtedly find an important place in this form of therapy. Although certain sulfa preparations are quite suitable for aerosol administration the results are generally disappointing. Iodide preparations may be administered by the aerosol route for fungous infections of the bronchi. In the treatment of bronchial infec-

frequently assumes pathogenic qualities or is at least responsible for protraction of the illness. Thus complication may be combated with aerosol iodide therapy. To achieve maximal clinical benefits from aerosol antibiotic therapy, the bacterial flora of the sputum should be carefully followed. A changing picture requires immediate modification of the therapeutic regimen. The management of each case must be integrated with the clinical signs and symptoms and laboratory findings. The possible and unpredictable variations in each disease and in each patient are impressive.

Laboratory sup

consideration and indicated utilization of other specific supportive, and symptomatic measures. Adequate control of exhausting cough may require the administration of small doses of anodynes such as 30 mg of codeine, or 15 mg of morphine. Whenever possible, suppression of the cough reflex should be attempted only after the correct diagnosis is established. Injudicious symptomatic therapy frequently masks the clinical picture of serious pulmonary diseases and lulls the patient and physician into a feeling of false security. Barbiturates and bromides are also effective in suppressing the cough reflex. When cough interferes with rest and sleep, the use of a suitable sedative or anodyne preparation is indicated. One-fourth to $\frac{1}{2}$ gram (15 to 30 mg) doses of

codeine are effective in the suppression of annoying coughs. The desirable clinical effects of codeine may be obtained following the administration of 1 or 2 teaspoonfuls of elixir of terpin hydrate with codeine (NF). This popular preparation supplies the added expectorant properties of terpin hydrate. Derivatives of belladonna should never be used to control cough or to diminish bronchial secretions. When useless cough results from the presence of tenacious sputum, the employment of expectorant drugs is indicated. Treatment with expectorant drugs is wholly symptomatic. Their usage dates back to antiquity. Of the many sedative and stimulant expectorant drugs ammonium chloride, ammonium carbonate, potassium citrate, potassium acetate, potassium iodide, sodium iodide, syrup of ipecac, creosote oil of eucalyptus oil of turpentine, syrup of hydriodic acid and terpin hydrate are the most popular. Inhalation of 5 to 10 per cent carbon dioxide for 5 to 10 minutes is an

pectorant qualities of the old-fashioned croup kettle should never be underrated. It is safe and effective. The author has obtained satisfactory results with the following expectorant mixture:

Ammonium chloride	3vss
Compound mixture of opium	3iv
and Glycyrrhiza (NF)	
(brown mixture)	

Two teaspoonfuls of this mixture are prescribed four times daily. In order to avoid the unpleasant side reactions, especially nausea and vomiting, it should be taken after meals and at bedtime. The addition of fruit juices makes the prescription more palatable. For sedative effects a barbiturate may be added. In cases with marked bronchial edema and spasm a sympathomimetic drug may also be added to this mixture. The simultaneous use of a suitable antihistaminic as a part of this mixture, or separately, is a desirable practice especially in cases of allergic bronchitis. Patients who cannot tolerate ammonium chloride and brown mixture in the recommended dosage should be tried on smaller doses or treated with one of the other expectorants. The intelligent use of a satisfactory expectorant, although only symp-

tomatic, is essential in the treatment of chronic bronchitis and bronchiectasis. Its value is twofold. By making the bronchial secretions more watery, it helps to abolish useless and exhausting cough. Likewise, effective expectoration of bronchial secretions permits aerosolized drugs to reach the most remote recesses of the bronchial tree. In order to avoid the possibility of accompanying secondary infection with *Candida*, the initial administration of an iodide may be indicated in conjunction with aerosol antibiotic therapy. After the maximal beneficial results of expectorant drugs or mixtures are obtained their continued administration is not only unnecessary but may actually mask and aggravate the clinical picture.

Other Therapeutic Procedures. In the management of bronchiectasis, *postural drainage* should never be neglected. The proper position can be determined after bronchography. To derive satisfactory results from this form of symptomatic therapy, the patient should be carefully instructed in the correct performance of this procedure. For the first few days careful personal supervision by the physician or trained assistant is necessary. Special postural drainage beds are available. The instillation of lipidol into the bronchial tree and bronchoscopic aspiration of tenacious secretions have their merit, but the resulting benefits are temporary. These practices are no longer popular forms of therapy. Bronchoscopic aspiration during a course of aerosol therapy, however, is helpful and facilitates the achievement of maximal symptomatic relief. Crushing of the phrenic nerve, the production of artificial pneumothorax and thoracoplasty have all been tried and recommended in the treatment of bronchiectasis. Only in the presence

of massive disease, however, does any of these measures, now seldom used, deserve serious consideration. Bismuth and arsenic should be used only in the presence of unusually large numbers of fus-

by the medical management of bronchiectasis are only temporary. Patients who are

exhausting cough. In cases of allergic bronchitis the use of aerosol benadryl results in dramatic clinical improvement. Those cases which fail to respond to systemic administration of antihistamines are benefited by aerosol administration. Varying concentrations of penicillin, tyrothricin, streptomycin, adrenalin, and benadryl in the desired amounts may be administered in the same aerosol solution.

Aerosol antibiotic therapy should be continued until the maximal beneficial response has been achieved. The number of daily treatments and the dosage of the antibiotic agent depend on the nature and severity of the illness and should be adjusted frequently to parallel the clinical and laboratory response. The chest roentgenogram should not be used as a barometer of therapeutic response since it does not necessarily parallel the clinical progress of the disease. Initially the more serious cases may require four daily treatments. In the presence of concomitant sinus infections which so frequently complicate the picture of chronic bronchitis and bronchiectasis, aerosol therapy by the nasal route should be carried on simultaneously. Both areas of infection must be controlled in order to obtain satisfactory results. Lingering infection in either area predisposes to infection of the other. The frequent association of sinusitis and chronic bronchitis has justified the existence of the descriptive term *bronchosinusitis*.

The intelligent use of aerosol antibiotic therapy in cases of chronic bronchitis due to infection will achieve not only striking palliative results but in many instances lasting cures. Systemic antibiotic therapy is unnecessary and useless once the extrapulmonary manifestations of the primary disease are controlled. The therapeutic management of the case may then be confined to the aerosol route. Aerosol therapy does not cure bronchiectasis. It affords effective symptomatic relief and is additionally valuable in the preoperative preparation of these patients for surgical excision of the involved pulmonary tissue. Furthermore, many patients who in the past would have been denied the benefits of surgical therapy because of their debilitated condition may now be converted into suitable candidates for surgery. Aerosol antibiotic therapy of

pseudobronchiectasis generally results in permanent cures.

Although this presentation primarily stresses the benefits of penicillin and streptomycin aerosol therapy, it is important to note that many other drugs can be prepared for use in this manner. As newer antibiotic agents are discovered and made available, many of them will undoubtedly find an important place in this form of therapy. Although certain sulfa preparations are quite suitable for aerosol administration, the results are generally disappointing. Iodide preparations may be administered by the aerosol route for fungous infections of the bronchi. In the treatment of bronchial infection,

frequently assumes pathogenic qualities or is at least responsible for protraction of the illness. This complication may be combated with aerosol iodide therapy. To achieve maximal clinical benefits from aerosol antibiotic therapy, the bacterial flora of the sputum should be carefully followed. A changing picture requires immediate modification of the therapeutic regimen. The management of each case must be integrated with the clinical signs and symptoms and laboratory findings. The possible and unpredictable variations in each disease and in each patient are impressive.

consideration and indicated utilization of other specific supportive and symptomatic measures. Adequate control of exhausting cough may require the administration of small doses of anodynes such as 30 mg of codeine or 15 mg of morphine. Whenever possible, suppression of the cough reflex should be attempted only after the correct diagnosis is established. Injudicious symptomatic therapy frequently masks the clinical picture of serious pulmonary diseases and lulls the patient and physician into a feeling of false security. Barbiturates and bromides are also effective in suppressing the cough reflex. When cough interferes with rest and sleep, the use of a suitable sedative or anodyne preparation is indicated. One-fourth to $\frac{1}{2}$ grain (15 to 30 mg) doses of

codeine are effective in the suppression of annoying coughs. The desirable clinical effects of codeine may be obtained following the administration of 1 or 2 teaspoonfuls of elixir of terpin hydrate with codeine (NF). This popular preparation supplies the added expectorant properties of terpin hydrate. Derivatives of belladonna should never be used to control cough or to diminish bronchial secretions. When useless cough results from the presence of tenacious sputum, the employment of expectorant drugs is indicated. Treatment with expectorant drugs is wholly symptomatic. Their usage dates back to antiquity. Of the many sedative and stimulant expectorant drugs ammonium chloride, ammonium carbonate, potassium citrate, potassium acetate, potassium iodide, sodium iodide, syrup of ipecac, creosote, oil of eucalyptus, oil of turpentine, syrup of hydriodic acid, and terpin hydrate are the most popular. Inhalation of 5 to 10 per cent carbon dioxide for 5 to 10 minutes is an

essential in the treatment of chronic bronchitis and bronchiectasis. Its value is twofold. By making the bronchial secretions more watery, it helps to abolish useless and exhausting cough. Likewise, effective expectoration of bronchial secretions permits aerosolized drugs to reach the most remote recesses of the bronchial tree. In order to avoid the possibility of accompanying secondary infection with *Candida*, the initial administration of an iodide may be indicated in conjunction with aerosol antibiotic therapy. After the maximal beneficial results of expectorant drugs or mixtures are obtained, their continued administration is not only unnecessary but may actually mask and aggravate the clinical picture.

Other Therapeutic Procedures. In the management of bronchiectasis, *postural drainage* should never be neglected. The proper position can be determined after bronchography. To derive satisfactory results from this form of symptomatic therapy, the patient should be carefully instructed in the correct performance of this procedure. For the first few days, careful personal supervision by the physician or trained assistant is necessary. Special postural drainage beds are available. The instillation of lipidol into the bronchial tree and bronchoscopic aspiration of tenacious secretions have their merit, but the resulting benefits are temporary.

pectorant qualities of the old-fashioned croup kettle should never be underrated. It is safe and effective. The author has obtained satisfactory results with the following expectorant mixture:

Ammonium chloride	3vss
Compound mixture of opium and Glycyrrhiza (NF)	3iv
(brown mixture)	

Two teaspoonfuls of this mixture are prescribed four times daily. In order to avoid the unpleasant side reactions, especially nausea and vomiting, it should be taken after meals and at bedtime. The addition of fruit juices makes the prescription more palatable. For sedative effects, a barbiturate may be added. In cases with marked bronchial edema and spasm, a sympathomimetic drug may also be added to this mixture. The simultaneous use of a suitable antihistaminic as a part of this mixture or separately is a desirable practice, especially in cases of allergic bronchitis. Patients who cannot tolerate ammonium chloride and brown mixture in the recommended dosage should be tried on smaller doses or treated with one of the other expectorants. The intelligent use of a satisfactory expectorant, although only symp-

tomatic, is essential in the treatment of chronic bronchitis and bronchiectasis. Its value is twofold. By making the bronchial secretions more watery, it helps to abolish useless and exhausting cough. Likewise, effective expectoration of bronchial secretions permits aerosolized drugs to reach the most remote recesses of the bronchial tree. In order to avoid the possibility of accompanying secondary infection with *Candida*, the initial administration of an iodide may be indicated in conjunction with aerosol antibiotic therapy. After the maximal beneficial results of expectorant drugs or mixtures are obtained, their continued administration is not only unnecessary but may actually mask and aggravate the clinical picture.

Other Therapeutic Procedures. In the management of bronchiectasis, *postural drainage* should never be neglected. The proper position can be determined after bronchography. To derive satisfactory results from this form of symptomatic therapy, the patient should be carefully instructed in the correct performance of this procedure. For the first few days, careful personal supervision by the physician or trained assistant is necessary. Special postural drainage beds are available. The instillation of lipidol into the bronchial tree and bronchoscopic aspiration of tenacious secretions have their merit, but the resulting benefits are temporary. Patients who are

suitable candidates for surgery should be given the benefit of segmental resection lobectomy or pneumonectomy. Excision of all the infected tissue is the only way to cure bronchiectasis. Nevertheless the best treatment of bronchiectasis is prevention of the disease. When physicians become familiar with its causes and pathogenesis this goal may be approached.

In the treatment of chronic bronchitis and bronchiectasis roentgen therapy has proved of some benefit in selected cases. Chronic cough which results from the mechanical effect of endothoracic tumors may be relieved by roentgen therapy if the tissue is radiosensitive. In selected cases autogenous bacterial vaccines of other responsible al-

lerts achieved in chronic bronchitis are permanent. Stock house dust vaccines are not so effective as dust vaccines prepared from the patient's own home. Vaccines may likewise be prepared from the patient's mattress and pillow stuffing. Only too frequently desensitization fails to accomplish its intended purpose. Some patients may be benefited by removal to a warm, dry climate. If extrinsic allergens have a role in the disease it may be possible to relocate in a geographic area free of the offending agent or agents. Chronic bronchitis due to irritating chemical or physical agents can best be treated by proper prophylaxis or avoidance of the noxious agent. No patient who suffers from chronic bronchitis or bronchiectasis should be permitted to smoke. Abandonment of this habit will yield gratifying symptomatic relief in bronchiectasis and may result in permanent

cures in chronic bronchitis. Patients with bronchial disorders should meticulously avoid sudden temperature changes and unnecessary exposure to inclement weather. The treatment of psychogenic cough is an exasperating problem in therapeutics willingly consigned to the psychiatrist.

In the management of chronic bronchitis and bronchiectasis careful attention should be given to the patient's general condition. Unless the general condition is improved and maintained at a satisfactory level all forms of treatment may be in vain. A high calorie, well balanced diet should be prescribed. The use of supplementary vitamins should be considered and is frequently indicated. Debilitated patients may require whole blood transfusions or intravenous amino acids. Absolute bed rest is rarely necessary except during febrile periods. Plenty of sunshine and fresh air are important. Chronic infections of the upper respiratory tract should be eliminated by either medical or surgical treatment. As long as there is any infection in the upper respiratory tract recurrence of bronchial disorders may be expected with monotonous regularity. Chronic bronchitis is often associated with cardiac decompensation and will be cured or markedly improved by improvement in the cardiac status.

Although the specific supportive and symptomatic therapy of chronic bronchitis and bronchiectasis has improved the suc-

LOUIS L. FRIEDMAN
SANDY B. CARTER

DISEASES OF THE LUNGS

EMPHYSEMA

The treatment of emphysema is entirely symptomatic. Relief of dyspnea and especially severe paroxysms of dyspnea is the major problem in the treatment of emphysema. The most one can expect from presently available and popular therapeutic measures is temporary relief of the clinical symptoms. No lasting benefits should be

expected. Successful treatment of primary diseases capable of producing emphysema is the best safeguard against its development.

Many cases of emphysema develop in asthmatic individuals. In these instances the effective management of the asthma will have a beneficial effect on the clinical manifestations of emphysema. The use of appropriate vaccines to desensitize these patients

is frequently quite effective in either diminishing or actually eliminating the allergic reactions. More recently in cases of emphysema associated with an allergic component the use of various antihistaminic preparations has proved successful. To obtain the maximal therapeutic benefits from the use of these new drugs administration should be by the aerosol route (see section on Chronic Bronchitis and Bronchiectasis). Especially in long standing cases systemic therapy is prone to result in failure. Aerosol antihistaminic therapy is capable of achieving the desired results both in cases with an allergic component and frequently in those due to other causes. Seven and one half grains (0.5 gm) of aminophylline administered in a 20 cc solution is likewise effective in relieving dyspnea associated with emphysema. The use of aminophylline by mouth is not as effective chiefly because the large dosage required by this route of administration is nauseating and cannot be tolerated by most patients. Results achieved with rectal suppositories of aminophylline 7½ grains (0.5 gm) are likewise discouraging. Some proprietary preparations contain a barbiturate in one form or another. The relief obtained with these combinations is probably due to the effect of the sedative. Properly prepared solutions of aminophylline are likewise effective by the aerosol route. Severe paroxysms of dyspnea may require the administration of oxygen. Some authorities on the subject of emphysema believe that a mixture of helium and oxygen therapy is more effective. Nevertheless the relief obtained with oxygen therapy is not only striking but frequently quite lasting.

The use of a sympathomimetic drug such as ephedrine sulfate ½ to 1 grain several times daily is generally effective. In the absence of acknowledged contraindications this drug may be administered to advantage. Likewise 1 cc of adrenalin in oil (1:500) given intramuscularly from one to three times daily may relieve a patient's distress.

preparations is indicated. One half to 1 cc of an alkali solution is given.

or aerosol adrenalin (1:100). Unfortunately

the administration of these drugs in sufficient dosage to achieve the desired therapeutic benefits predisposes to annoying side reactions. Insomnia and tachycardia are only a few of the more undesirable side effects. The routine use of a sedative drug should be the rule when large doses of sympathomimetic drugs are used. In this manner the clinical manifestations of the undesirable side reactions may be masked. Many varieties of sympathomimetic agents are available. Any one of these preparations can be used with equal benefit. Undesirable side reactions occur with all of these drugs when clinically effective amounts are prescribed. Pharmaceutical companies have tried to eliminate these annoying complications. Sympathomimetic drugs should not be used continuously for more than brief periods of time. Prolonged use of these agents eventually renders the patient resistant to their beneficial pharmacologic actions. The prolonged use of aminophylline is attendant with the same limitations. The best results will be accomplished by varying the drugs used and the route of administration.

In acute episodes of dyspnea the use of a barbiturate, a bromide or any other satisfactory sedative in adequate amounts to relieve the omnipresent apprehension of the patient is imperative. This is an important admonition since this undesirable psychogenic reaction aggravates all of the clinical symptoms, especially dyspnea. The use of morphine and other opiates is contraindicated in patients whose emphysema complicates asthma.

Variable results may be obtained with the use of abdominal binders as described by Alexander Kountz and Kerr. They are prescribed on the assumption that dyspnea may be relieved by increasing the intra abdominal pressure. Many patients cannot tolerate these belts and readily forego the possible symptomatic benefits. Abdominal belts should be recommended however only after fluoroscopic examination has ascertained the degree of diaphragmatic mobility. The prevention and effective treatment of bronchitis are of utmost importance in the therapeutic management of emphysema. A combination of benzydol, adrenalin, penicillin and streptomycin or tyrothricin administered by the aerosol route is exceptionally effective when

emphysema and chronic bronchitis coexist. A more detailed discussion of this phase of the treatment is given in the section on emphysema and chronic bronchitis.

Bronchiectasis. Regardless of the various therapeutic measures in emphysema, the ultimate prognosis is poor.

LOUIS L. FRIEDMAN
SANDY B. CARTER

PULMONARY FIBROSIS

Pulmonary fibrosis may result from any acute or chronic disease of the pleura or bronchopulmonary tissue. With the onset of symptoms due to fibrosis of pulmonary tissue the severity of the disease is usually progressive. There is no effective therapy for this condition. Therapeutic measures are capable of effecting only temporary symptomatic relief. The most frequent clinical manifestations of the disease are chronic cough, foul sputum, cyanosis, dyspnea, and recurrent bronchopulmonary infections. Management of the disease depends entirely on the nature of the prevailing clinical symptoms and their severity. Systemic administration of the various chemotherapeutic and antibiotic agents is ineffectual. Destruction of the normal pulmonary architecture, especially the vascular network, is responsible for this failure. The best results are obtained from the use of indicated aerosol therapy. This therapeutic measure, although only palliative, affords effective relief of annoying symptoms. The ultimate survival prognosis is influenced favorably by the use of aerosol antibiotics for the control of secondary infections. Bronchial infections and dyspnea will respond to the measures described in the sections on Chronic Bronchitis, and Bronchiectasis and Emphysema, respectively.

Likewise, the same general supportive and symptomatic considerations are applicable in this condition. Every effort should be made to prevent secondary infection and to maintain a satisfactory state of general health. Pulmonary fibrosis, however, is more apt to result in heart failure than either chronic bronchitis or bronchiectasis. When this complication develops, the usual methods of restoring and maintaining the failing cardiac reserve are indicated. Since the treatment of

pulmonary fibrosis is so unsatisfactory, the best approach to the problem appears to be energetic and effective therapeutic management of the primary diseases from which it may develop.

LOUIS L. FRIEDMAN
SANDY B. CARTER

COLLAPSE OF THE LUNG, ATELECTASIS

The rational and successful treatment of pulmonary collapse depends on rapid accurate determination of the cause and extent of the collapse. The principles of prevention

will vary according to the type and cause. Pulmonary collapse is divided into two main types, simple and massive. If the collapse is limited to a few alveoli or lobules it is termed simple. Massive collapse includes the more extensive cases in which there is involvement of one or more lobes, even a complete lung. This classification considers merely the amount of pulmonary tissue involved, but it can be readily appreciated that massive collapse will call for more energetic measures than collapse of a few alveoli or lobules. The treatment of pulmonary collapse will be more effective if the cause of the collapse is known. For instance, treatment would be different in cases due to compression from pleural effusion or spontaneous pneumothorax from those due to obstruction of the bronchi or bronchioles. The same etiologic factor may be responsible for either simple or massive collapse, depending entirely on the amount of pulmonary tissue involved.

Pulmonary collapse is usually the result of occlusion of one or more bronchi or bronchioles. The most frequent cause of such obstruction is the presence of some condition which produces an increase in bronchopulmonary secretions combined with interference of the cough reflex. Chemical

associated with complicating atelectasis are surgical procedures and trauma. Preoperative and postoperative sedatives and anesthetics, anesthetic agents, shock, nervous factors, and

aspirated material all predispose to this serious complication. Other causes of atelectasis include pulmonary embolism, infarction, tumor, allergy and extrapulmonary pressure.

The three important considerations in the treatment of pulmonary collapse are prevention, removal of the endobronchial obstruction and attention to the secondary results of atelectasis. In many patients, particularly those with simple collapse, treatment is seldom required and the atelectasis is frequently overlooked clinically. The reason for this is that a large number of postoperative patients suffering from atelectasis will unintentionally clear the secretions from the bronchi and re-expand the collapsed portion of the lung by reflex deep breathing and coughing. There are numerous prophylactic measures that should be observed, especially in patients who from past experience are known to be more susceptible to pulmonary collapse, such as the aged, the very young, the debilitated, the postoperative patient (particularly after abdominal or thoracic surgery) and those who have been victims of serious traumatic injuries. Operations should be postponed for two or three weeks following infections of the mouth and respiratory tract because of the increased danger of accumulating tenacious secretions. The choice of anesthetic and preoperative and postoperative medications plays some part. For instance, ether irritates the bronchial mucous membrane and causes increased secretion, as compared with various gases

the use of suction when indicated or by proper postural position. In the immediate postoperative period after all major surgical procedures and regardless of the anesthetic used, a mixture of oxygen (90 per cent) and carbon dioxide (10 per cent) should be administered routinely for 1 to 10 minute periods at regular frequent intervals. The use of deep breathing exercises, frequent changes of position, avoidance of deep narcotization and of tight thoracic and abdominal binders are other recommended prophylactic measures. Discreet early ambulation increases pulmonary activity and consequently, prevents accumulation of secretions. It is to be emphasized that the cough reflex must be encouraged and not suppressed. Careful nursing is important in both the prophylaxis and treatment of atelectasis. From experience gleaned in other conditions, we feel that parenteral and aerosol antihistaminics may be of real prophylactic and possibly therapeutic value.

The treatment of pulmonary collapse is both symptomatic and specific. Control of pain and dyspnea may be accomplished with the use of a suitable sedative in adequate dosage. Barbiturates and bromides are popular. If these are found to be inadequate, the use of oxygen and an opiate such as morphine may be required.

to 1 mg) to $\frac{1}{4}$ grain (15 mg) doses hypodermically may be required to relieve pain and dyspnea. This may be repeated as often as necessary if the respiration remains 16 per minute or over. Cheyne Stokes breathing must always be avoided. A sitting or semi-sitting position will usually be more comfortable. Breathing a mixture of 90 per cent oxygen and 10 per cent carbon dioxide for 5 to 10 minutes every hour will stimulate respiratory rate and depth and produce more watery secretions. This practice is more effective in prophylaxis than in treatment. Fluid balance must be maintained during the emergency until the patient is able to satisfy his own requirements.

In most cases of significant pulmonary collapse there is an endobronchial obstruction which demands immediate removal. It is necessary that the bronchi be cleared within a few hours after the development of

reflex bronchoconstriction and to diminish bronchial secretions by the use of atropine. The cough reflex is restricted by pain and suppressed by opiates. Judicious use of only minimal amounts of opiates is therefore recommended. Smoking irritates the respiratory tract and should be forbidden in the immediate postoperative period. The bronchial secretions are made more serous by humidification of the air and by the use of iodides and alkalis. Patients should not be exposed to chilling or drafts. Aspiration of vomitus, saliva and mucus should be prevented by

atelectasis if complete and rapid re expansion is to be achieved. If the obstruction is due to reflex bronchial spasm, good results may be obtained with the intravenous injection of $\frac{1}{2}$ to 1 grain of atropine sulfate or 1 grain of papaverine hydrochloride. The use of intravenous aminophylline and calcium gluconate may be of some value. Symptomatic drugs are likewise frequently beneficial. If the simpler measures such as postural drainage are not effective, intrabronchial catheterization with subsequent aspiration or bronchoscopic aspiration may be necessary. Postural drainage is accomplished by placing the patient in a position with the involved lung uppermost. Retained secretions will gravitate downward, stimulate the mucosa, and the resulting cough may be sufficient to expel the obstructive material. Occasionally, when conditions permit, a moderate fistic assault on the thorax by the physician or a rather intense shaking of the patient will result in relief of the obstruction. This practice is not recommended routinely. Intrabronchial catheter aspiration can be used to remove aspirated vomitus, mucus, and saliva. This can be done at the bedside. By turning the patient from side to side, the catheter can be passed into each bronchus and suction applied. Some feel that blind suction by catheter may cause serious damage by its traumatic effects. In the absence of a competent bronchoscopist, however, intrabronchial catheter aspiration assumes a prominent role in the treatment of atelectasis. Suction drainage under direct vision of the bronchoscope is, nevertheless, the most efficient and least traumatic type of aspiration. It offers visual assurance that the main bronchi have been cleared. Furthermore, it assures adequate suction without trauma and provides an opportunity to apply shrinking solutions to areas of edema.

Bronchoscopy is particularly valuable in (1) postoperative patients who through pain or debility are unable to remove obstructing secretions from the bronchi, (2) unconscious patients and those who have suffered injury to the nervous mechanism controlling the cough reflex, such as occurs in lesions of the cervical portion of the spinal cord or in injuries to the midbrain, (3) patients with injuries involving the airway with aspiration of blood or other foreign material.

ou
ple

the relief of pain and dyspnea, can frequently be obtained by artificial pneumothorax. Enough air is introduced into the pleural space on the side of the collapse to restore the intrapleural pressure to a normal negative reading. It must be remembered, however, that any offending obstruction must be removed before re expansion of the lung will take place.

The secondary results of atelectasis must be considered because of the omnipresent danger of infection, particularly bronchopneumonia. The drug of choice in most cases is penicillin which can be administered parenterally. Aerosol therapy is useful in bronchial infections (see section on Chronic Bronchitis and Bronchiectasis). A single daily injection of 300,000 units of one of the long acting penicillin preparations is adequate. The choice of a chemotherapeutic and antibiotic agent and the route of administration all depend on the nature of the infection and therapeutic response.

In summary, the treatment of pulmonary collapse consists of prophylactic measures, actual treatment, and attention to the secondary results. The most effective prophylactic measures are those which prevent respiratory tract infections, excessive bronchial secretion, and stimulate the cough reflex. In treatment, removal of the offending endobronchial obstruction is the main consideration, and bronchoscopy is the method of choice if simpler measures are not effective. Secondary infection is usually best managed by the use of penicillin.

LOUIS L. FRIEDMAN
SANDY B. CARTER

PULMONARY EMBOLISM

It was formerly believed that pulmonary embolism was invariably the sequel either of abdominal or pelvic operations or of injuries such as fracture of the hip. It is now known that pulmonary embolism is often a complication of any condition, surgical or medical, in the treatment of which the patient is necessarily confined to bed or immobilized for prolonged periods of time. Any chronic, debilitating disease, particularly in the aged

and asthenic, may be complicated by pulmonary embolism. Into this category would fall such conditions as inoperable tumor, cerebral vascular accident, paralysis from any cause, marked malnutrition, and advanced senility. Trauma of the vascular system may produce thrombus formation and subsequent embolism. In recent years, considerable stress has been placed on thromboembolic phenomena following myocardial infarction. However, in spite of the more frequent recognition of thromboembolic complications in medical patients, they are still most often encountered in postoperative and traumatic states. Why does thromboembolism occur in these postoperative, traumatized, and bedridden patients? It has been postulated that, following surgical procedures and trauma, a substance is liberated which increases blood viscosity and the tendency to intravascular clotting. Of prime importance, however, is the slowing of circulation and stasis which occur when prolonged bed rest becomes necessary. While the patient is at rest there is a physiologic decrease in cardiac activity and subsequent slowing of the circulation. During normal activity blood flow through the lower extremities is assisted by muscular contraction and pressure on the veins which forces blood back toward the heart. Deep breathing, resulting from unusual physical activity, produces an increase in intrapleural negative pressure which helps to maintain an adequate circulatory rate. Any interference with circulation, either by diminution of the normal physiologic forces or by mechanical obstruction of the venous return, may lead to stasis and subsequent thrombus formation. Most attention in the prevention and treatment of pulmonary embolism is focused on the lower extremities. The reason for this is that the most common site of phlebothrombosis, subsequent to interference with circulation, is in the deep veins of the leg, and most cases of pulmonary embolism are secondary to phlebothrombosis of these veins.

Prophylaxis. Therapy of pulmonary embolism is both prophylactic and specific. Until recent years therapeutic measures were all most entirely symptomatic. Within the span of a few years three advances have been made in the treatment of pulmonary embolism. These are ligation of the involved veins,

early ambulation following major surgical procedures, and anticoagulant therapy. All

prevention = maintenance of adequate circulation. Patients who must remain in bed,

must be done even at the risk of alarming the patient. Mental discomfort is still preferable to a serious illness or possible death. The patient or trained attendant should be instructed in the use of preventive measures

knees partially flexed by a supporting pillow or by folding the hospital bed is recommended frequently for the comfort of the

sure on the veins and interferes with the return of the blood from the lower extremities.

The patient must be instructed in appropriate muscle exercises of the lower extremity. At least three times daily the patient should observe a regular exercise period consisting

of the lower extremities. Another way to increase muscle tone of the lower extremities is to elevate the head of the bed about 6 inches. In order to avoid sliding downward, the patient pushes against a well positioned footboard. This produces the desired exercise effect. Deep breathing exercises are also required at regular intervals. Six to ten forced inspirations and expirations every hour or so are effective. There has been a great reduction in the incidence of pulmonary embolism since the institution of early ambulation following major surgery, childbirth, hip fractures, etc. The activity of ambulation maintains circulation. By ambulation is meant active walking and exercise and not merely sitting in a wheelchair. The

latter is a dangerous practice because of the pressure on the vessels from the flexed joints. Other prophylactic measures include prevention of shock, avoidance of hemoconcentration and maintenance of cardiac output.

Finally prophylaxis includes venous ligation and anticoagulant drugs. When used in the treatment of pulmonary embolism these procedures are really prophylactic steps to prevent additional and possibly fatal emboli

develop this condition and of preventing recurrent pulmonary embolism in patients who have already experienced a nonfatal episode of embolism. In elderly patients who are confined to bed or must undergo major surgery venous ligation is often recommended before or at the time of operation. This will prevent emboli from anticipated phlebothrombosis of the deep leg veins. The same step is often taken in the presence of hip fractures in the aged. Following myocardial infarction dicumarol is recommended in the majority of cases until activity is resumed. This is primarily intended to prevent the development of phlebothrombosis of the deep leg veins to prevent extension of the thrombus in the coronary arteries and to prevent the development of a mural thrombus.

Active Treatment. Once pulmonary embolism has occurred it must be treated heroically energetically and without procrastination. Every effort must be exerted to prevent additional thromboembolic phenomena. Prevention is the most effective form of treatment.

It should be given intravenously to relieve the pain. Morphine or some other suitable narcotic is often

adequate. 3 grains (90 mg.) of papaverine hydrochloride and $\frac{1}{150}$ grain of atropine sulfate administered hypodermically are recommended for the relief of reflex vascular and bronchial spasm. Papaverine and atropine should be administered hypodermically for several days at 4 hour intervals but after the emergency has passed oral administration will suffice.

For relief of dyspnea oxygen should be

administered by nasal catheter mask or tent. If shock supervenes it must be combated with the measures already outlined above and by cautious infusions of whole blood or plasma. The results of embolectomy in pulmonary embolism are discouraging and the procedure as a rule fails to achieve its therapeutic goal. Occasionally a rare success is reported from institutions with well organized "embolectomy teams."

When a patient has recovered from pulmonary embolism the major problem is the prevention of a second episode which may prove fatal. Both venous ligation and anticoagulants have their proponents. Ligation will only prevent emboli from sources distal to the ligation whereas anticoagulants usually prevent additional thrombosis throughout the body. Ligation of veins is superior

to emboli from the leg veins are difficult to prevent with anticoagulants since they occur at irregular and unpredictable intervals. Venous ligation is also the treatment of choice when anticoagulants are contraindicated and when they are ineffective. In the majority of cases anticoagulant therapy is preferable. To be effective venous ligation must be proximal to the thrombus. When the thrombus is in the plantar or deep leg veins superficial femoral vein ligation distal to the profunda is recommended. If the thrombus is higher it may necessitate ligation of the common femoral vein, common iliac vein or even the inferior vena cava. Each of these vessels has been ligated successfully but the higher the ligation the more difficult the procedure and the less likely the development of subsequent adequate collateral circulation.

The anticoagulants heparin and dicumarol are most often used for the prevention of original or recurrent pulmonary embolism. When the possibility of thromboembolic phenomena is recognized early dicumarol alone is usually adequate because an effective reduction of prothrombin concentration can be accomplished before the danger becomes manifest. On the other hand when pulmonary embolism has already occurred a rapid anticoagulant effect must be obtained. The combined use of fast acting heparin as well

PNEUMOCONIOSIS

blood dyscrasias with bleeding tendencies, ulcerative lesions or open wounds, and recent operations on the brain and spinal cord. If for any reason the anticoagulant effect becomes undesirable or dangerous, heparin can be neutralized by intravenous protamine or the hypoprothrombinemia produced by dicumarol usually can be raised to a safe level by the repeated intravenous use of large doses of vitamin K or vitamin K oxide and whole blood transfusions. Donors, previously prepared with large doses of vitamin K, are preferable if available. Before anticoagulant therapy is instituted a prothrombin concentration is determined. Fifty milligrams of heparin are then injected intravenously every 4 hours until the slowly acting dicumarol produces the desired reduction in prothrombin concentration to a level 30 to 50 per cent of normal. Heparin should then be discontinued. There are other ways of giving heparin but this is the most convenient.

Unless alarming, febrile reactions to heparin may be ignored. At the same time that heparin therapy is started, a single dose of 300 mg of dicumarol is given by mouth. On each subsequent day of therapy, a prothrombin concentration is determined on blood obtained at least 3 hours after heparin injection for as long as it is used. On those days that the prothrombin level is above 30 per cent, 200 mg of dicumarol are given. If the prothrombin concentration is below 30 per cent, no dicumarol is given. An average dose is 200 mg. Some patients require more, and others less, depending on the individual response. The object of treatment with dicumarol is to maintain the prothrombin concentration between 10 and 30 per cent. Some feel that a reduction of prothrombin concentration to 40 or 50 per cent is adequate to prevent thromboembolic phenomena and the danger of complicating hemorrhage is thereby reduced. During anticoagulant therapy, frequent urinalyses and other indicated clinical and laboratory examinations should be performed daily in order to discern the first evidence of a complicating hemorrhagic response.

LOUIS L. FRIEDMAN
SANDY H. CARTER

Pneumoconiosis results from the inhalation of certain dusts over a long period of time. It is characterized by the development of proliferative and fibrotic changes in the lungs. The most important dust diseases of the lung are anthracosis, asbestosis, and silicosis.

Anthracosis (coal miner's lung) is rarely associated with any significant impairment of health or with physical disability. It is felt that advanced anthracosis is not only unrelated to the development of tuberculosis but may actually prevent this disease. Anthracosis, however, renders the individual more susceptible to pneumonia. The major problem in connection with anthracosis is the prevention of infection. Uncomplicated anthracosis requires no treatment unless it produces an unusual degree of pulmonary fibrosis.

Asbestosis is a form of silicosis which results from the inhalation of asbestos dust. This dust is primarily composed of magnesium silicate. Its association with pulmonary tuberculosis is not common. The condition predisposes to chronic bronchitis, bronchiectasis, emphysema, and bronchopneumonia. The treatment of these conditions is discussed above. Since there is no treatment for asbestosis, suitable and necessary prophylactic measures designed to prevent its development should be instituted during the processing of asbestos from the crushed mineral.

Of the dust diseases, silicosis is the most

valuable of aluminum dust in silicosis. Insufficient time has elapsed to evaluate this measure.

peutically. The prophylactic use of aluminum dusting will require more investigation before it is accepted or rejected. It has some serious drawbacks. Large concentrations of aluminum powder exert a harmful effect on cases of active or inactive pulmonary tuberculosis. Furthermore, its routine adoption in industries with a silicosis hazard may pre-

dispose to relaxation of proved and effective prophylactic measures

As in asbestosis, since there is no treatment for silicosis, prevention of the disease deserves special attention. It is the responsibility of industry to institute proper prophylactic measures in all occupations associated with a silicosis hazard. In addition, employees should be made familiar with the risks involved and educated in the maintenance of satisfactory prophylactic standards. A competent sanitary engineer should be employed to supervise the program of prophylaxis in all industries with a silica hazard. With the use of such instruments as the Greenburg Smith impinger, the electrostatic precipitator, the konometer, and the Owens jet, the total number and size of the silica particles can be determined. When the limits of the safety are exceeded, suitable prophylactic measures should be instituted immediately. Up to 5 000 000 particles of silica dust per cubic foot is considered a safe concentration.

Proper prophylaxis depends on the use of good housekeeping, proper ventilation and wet methods. The use of specially devised respirators is effective. Many workers, however, would rather chance the ultimate consequences of prolonged exposure to silica than wear the respirators. There are several methods of employing water or other liquids prophylactically. Water may be used to suppress dust at its origin as in wet drilling. It may be used as a spray to remove the hazardous dust from the air. Redispersal of the dust may be prevented by keeping all walls, floors, and other surfaces wet. In order to be effective, this measure must be practiced without relaxation. Frequent, regular determinations of the effectiveness of the selected safeguard are necessary in order to insure proper prophylactic control. On the surface, the financial expenditure involved in providing safe places of employment may appear formidable, impossible, and economically unsound. In actual practice, however, proper prophylaxis pays added dividends to the employer while safeguarding the health of the employee. Only rarely is it impossible to control the silica hazard.

Pre-employment roentgen examinations of the chest should be a routine requirement before engaging an employee for an occu-

evidence of any pulmonary disease especially active or inactive tuberculosis, should never be employed. Likewise, the employment of positive tuberculin reactors should be avoided. Inhaled silica has a deleterious effect on pulmonary tuberculosis. Follow up roentgen studies are the only means of detecting silicosis in its earliest stages. As soon as evidence of silicosis is detected in the roentgenogram, the employee should be transferred to an occupation free of silica dust. When this precaution is observed, the incidence of disabling and advanced silicosis may be expected to decline. It is important to recognize silicosis in the asymptomatic stage. When clinical symptoms develop, the course of the disease is usually progressive. Of added importance is the fact that silicosis predisposes to pulmonary tuberculosis. This complication occurs by various estimates, in from 65 to 95 per cent of the cases. The development of silicotuberculosis heralds a fatal outcome. It is the most serious complication of silicosis and, with rare exception, is refractory to all forms of available tuberculosis therapy.

Chronic bronchitis, bronchiectasis, emphysema, and pulmonary infections regularly complicate silicosis. The treatment of these secondary conditions is outlined under the respective sections dealing with these diseases. Again it must be stressed that aerosol therapy with various chemotherapeutic and antibiotic agents is preferable to systemic administration. General supportive and symptomatic measures are essentially the same as for other bronchopulmonary diseases.

LOUIS L. FRIEDMAN
SANDY B. CARTER

PULMONARY ABSCESS

Many pulmonary abscesses heal spontaneously. A large number respond to conservative medical management, a few require surgical intervention, and a very small number respond to no treatment at all. The intelligent use of sulfa drugs and antibiotic agents in those conditions which may be responsible for the development of a lung abscess has unquestionably reduced the inci-

dence of this complication. The sulfonamides have greater prophylactic than therapeutic value. The antibiotic agents, particularly penicillin, however, exert therapeutic as well as prophylactic effects. The prophylactic use of sulfa drugs or antibiotic agents in connection with surgical procedures involving infected areas of the head or neck is mandatory. Recent evidence has been accumulated which suggests the prophylactic superiority of the combined use of aerosol antibiotic with the simultaneous administration of a suitable sulfa drug or antibiotic systemically. When prophylaxis is limited to the systemic

bility of limiting prophylaxis to the use of aerosol antibiotics is receiving attention at this time, and the early results are encouraging.

Although the systemic administration of large doses of indicated antibiotic agents over long periods of time has cured many cases of lung abscess, aerosol antibiotic therapy is the treatment of choice. The use of systemic

trolled, aerosol antibiotic therapy may be relied upon to achieve any of the possible therapeutic benefits. A complete discussion of aerosol therapy may be found in the section on Chronic Bronchitis and Bronchiectasis. Direct bronchoscopic instillation of therapeutic agents into the abscess cavity has its advantages. When the bronchus leading to the abscess cavity is blocked by a tenacious exudate, bronchoscopic aspiration and instillation of the indicated antibiotic agent merits serious consideration. In the presence of a patent bronchus, bronchoscopic instillation need not be considered since aerosol therapy will achieve at least equal, if not better, results. Bronchoscopic instillation of concen-

complicating bronchiectasis. Choice of a suitable antibiotic agent is determined by the nature of the responsible micro-organism and the general bacterial flora. To achieve the best results, the therapeutic benefits of

aerosol therapy should be evaluated daily. In the treatment of lung abscess, the daily amount and gross characteristics of the sputum are important guides. Detailed and specific information can be obtained from bacteriologic studies. Frequent roentgen examinations of the chest and daily evaluation of the patient's clinical progress will also reflect the success or failure of the therapeutic

cal and laboratory evidence.

The success or failure of aerosol therapy in the treatment of lung abscess depends on the use of other important therapeutic measures. Correct postural drainage two or three times daily is absolutely necessary. The use of expectorant drugs is useful in maintaining bronchial patency and in relieving useless cough. When fusospirochetal organisms are present in large numbers, the use of an arsenical or bismuth may speed recovery. Iodides are necessary to eliminate the *Candida*. The use of pneumothorax is dangerous and is mentioned only for condemnation.

Phrenic crush, however, may prove helpful. Vaccine treatment and roentgen therapy are valueless. Amebic abscesses of the lung usually respond to specific amebicidal therapy. The drug of choice is emetine hydrochloride or chloroquine. One gram of emetine may be administered hypodermically for a period of 10 days. This is a dangerous drug and should be used with caution. It is contraindicated in patients with myocardial disease. Careful evaluation of the cardiac status including, especially, an electrocardiogram should be carried out before, during, and after each course of therapy. Neuritis is another important toxic effect of emetine. Large doses of thiamine chloride should be prescribed when emetine is used.

instance in which massive systemic sulfa drug and antibiotic therapy are indicated and imperative.

In order to be successful with the medical management of lung abscesses, careful attention must be given to the patient's general condition as well as to the local disease.

Frequent blood transfusions are beneficial. A high caloric nutritious diet should be prescribed. Those patients who suffer from anemia are not only candidates for blood transfusions but should also receive intravenous vitamin (min.)

Well managed aerosol therapy will usually result in the cure of acute lung abscesses and the prevention of most secondary manifestations such as bronchiectasis and fibrosis. Although it may be tried in chronic abscesses the results are disappointing. Aerosol therapy however should be used in an effort to convert debilitated patients and unfavorable cases into satisfactory surgical risks. Surgery should be recommended in all cases which

fail to respond to a satisfactory trial with conservative medical therapy. Unnecessary procrastination predisposes to a poorer prognosis and further complications. The use of aerosol therapy preoperatively and postoperatively will minimize the risk of surgery and the possibility of serious complications. Unprejudiced co operation between the internist and surgeon is essential for the successful management of all lung abscesses. Following spontaneous resolution medical cures and surgical drainage frequent follow up roentgen examinations are necessary. Pulmonary abscesses have a notorious habit of recurring even after months of inactivity and apparent cure.

LOUIS L. FRIEDMAN
SANDY B. CARTER

DISEASES OF THE PLEURA AND PLEURAL CAVITY

ACUTE PLEURISY

Effective symptomatic relief of pain is the first objective in the treatment of pleurisy. The generous use of $\frac{1}{2}$ grain (15 mg.) of morphine or $\frac{1}{2}$ grain (30 mg.) of codeine is generally necessary to produce the desired analgesia in the early stages of the disease. As the inflammatory reaction in the pleura subsides the use of milder analgesics such as acetylsalicylic acid will afford adequate control of pain. Disappearance of the patient's apprehension and sense of impending disaster parallels the symptomatic relief of pain. The marked improvement in the patient's general condition which accompanies satisfactory analgesia is truly dramatic. Immobilization of the affected hemithorax results in added clinical benefits. This may be accomplished by strapping the affected side with adhesive tape or application of a tight binder to the entire thorax. Proper immobilization requires the application of these restraining devices during full expiration. The patient should be instructed to lie on the affected side. Additional benefit is obtained by placing a pillow under the involved hemithorax. Injection of the intercostal nerves over the area of pleurisy with an anesthetic agent such as procaine, cocaine or novocain may also provide effective relief of pain.

We feel that the intravenous administra-

tion of calcium gluconate often produces satisfactory analgesia in pleuritis. Ten cubic centimeters of a 10 per cent solution (1 gm.) is the recommended dose. The use of a hot water bottle is always comforting. Although these measures may have a place in the control of pleuritic pain the use of a satisfactory narcotic is always indicated and imperative. The excruciating pain of pleurisy predisposes to voluntary restriction of respiration and frequently results in self produced dyspnea and cyanosis. Until adequate relief of pain is accomplished the use of oxygen may be necessary.

Only tuberculous pleurisy may be primary. This disease is discussed elsewhere in this book. All other inflammatory reactions of the pleura are secondary to local thoracic distant or generalized diseases. The treatment of pleurisy complicating these primary diseases for which there is no specific therapy is entirely symptomatic. Aside from the symptomatic relief of pain, dyspnea, cyanosis, cough and apprehension, satisfactory treatment of fibrinous pleuritis depends entirely on the correct therapeutic management of the primary responsible disease. Of the multitude of clinical entities which may cause pleurisy relatively few respond to specific drug therapy. The widespread use of sulfa drugs and antibiotic agents in the treatment of pulmonary and other infections

has resulted in a diminished incidence of clinical pleurisy

LOUIS L. FRIEDMAN
SANDY H. CARTER

PLEURISY WITH EFFUSION

Aside from the added problem of fluid in the pleural cavity the treatment of sero fibrinous pleurisy is similar to the management of fibrinous pleurisy. As a rule it is inadvisable to aspirate serofibrinous effusions unless the responsible agent is drug sensitive. Careless thoracentesis may convert a relatively harmless serofibrinous effusion into a troublesome empyema. In the presence of massive effusions resulting in marked dyspnea thoracentesis is indicated. Aspiration of the pleural cavity should be preceded by careful localization of the fluid. This can be accomplished with the aid of physical signs, roentgen examination in various positions and fluoroscopy. In spite of all possible precautions unsuccessful and traumatic thoracentesis may be encountered. Even large effusions may be difficult to locate with the

This has the effect of allaying apprehension

event of an untoward reaction

The use of sympathomimetic drugs such as epinephrine hydrochloride in these emergencies is fraught with danger and is contraindicated.

Thoracentesis is best accomplished with the patient in a sitting position. A high back rest or the lateral decubitus position may be necessary for those patients who are unable to maintain sitting posture. The skin is properly sterilized and the patient carefully draped as for a surgical operation. Using a small needle the skin at the site of the puncture is infiltrated with a local anesthetic such as 1 to 1 per cent procaine. After infiltration of the skin the needle is introduced deeper into the subcutaneous tissues, injecting the anesthetic as the needle is slowly pushed forward. When one is certain that the anesthetic

has been introduced as deep as the pleura the small needle is withdrawn. A large 18

lower rib in order to avoid injury to the intercostal artery and nerve. The needle should be slowly forced into the pleural cavity with great care in order to avoid injury to the underlying lung. If a bloody tap occurs it is wise to withdraw the needle and attempt the aspiration in another location.

When one is certain the pleural cavity has been entered careful aspiration with a 20 to 50 cc syringe is attempted. One must be

tached to the syringe. When the valve is turned one way the fluid from the syringe can be ejected into a suitable container. When the valve is turned back more fluid may then be aspirated from the pleural cavity. Successful withdrawal of thick exudates is accomplished more easily and safely after normal saline is instilled into the pleural cavity.

The intrapleural use of heparin to decrease fibrin formation requires additional investigation before its utilization can be recommended. Streptokinase may also prove to be of value.

There is no definite rule regarding the amount of fluid which may be aspirated. It is a good practice to remove all the fluid possible before signs of cardiorespiratory distress supervene. When the patient complains of a "pulling" sensation in the chest, dyspnea or coughs slightly thoracentesis must be terminated. These symptoms are the result of a too rapid re-expansion of the collapsed lung or a shifting mediastinum with consequent torsion of the great vessels at the base of the heart. The introduction of a small amount of air will relieve the symptoms and also provide more satisfactory roentgen ray and fluoroscopic localization of the fluid. In non-tuberculous effusions replacement of the aspirated fluid is contraindicated and should be avoided whenever possible. Only in the event of tuberculous pleurisy with demonstrable roentgen evidence of underlying pulmonary tuberculosis should a pneumothorax be established at the time of thoracentesis.

Should pleural adhesions follow resorption of the exudate as they frequently do, the induction of a therapeutic pneumothorax at a future date will be difficult or impossible to accomplish. Before the aspirating needle is withdrawn 50 000 units of penicillin should be instilled prophylactically in an effort to prevent secondary infection. To avoid draining sinuses the site of entrance should be massaged briskly, and the patient should be encouraged to lie on the affected side for several hours. The latter suggestion may be impossible to observe in the presence of marked dyspnea. Subsequent aspirations, if necessary, should be performed at other sites in order to avoid local complications. When the needle is in place, the patient must never be permitted to move the arm on the ipsilateral side. Pulmonary laceration may result or the needle may be broken.

If the serofibrinous effusion is due to a penicillin sensitive organism, 50 000 units of this drug may be instilled daily, or twice daily, until the fluid is sterile on seven successive cultures or the effusion is resorbed. Once a serofibrinous exudate resorbs, it does not tend to recur. The introduction of con-

in the pleural cavity, it will act as a diluent for the penicillin. Otherwise it is best to dissolve the penicillin in normal saline in such proportions that the resulting solution will not contain more than 500 to 1000 units per cubic centimeter. If the organism is penicillin resistant, streptomycin may be substituted. As much as 500 000 units may be instilled once or twice daily. The concentrations of streptomycin should not exceed 10 000 units per cubic centimeter. Simultaneous administration of systemic chemotherapeutic and antibiotic agents is necessary to obtain a lasting cure. Both penicillin and streptomycin are absorbed from the pleural cavity. General drug allergy has been observed after the intrapleural use of these drugs without concomitant or previous administration. To accelerate recovery from this complication the pleural cavity should be thoroughly washed with a solution of normal saline.

Prior to the era of antibiotics, it was the general tendency, for various reasons, to

avoid aspiration of both bacterial and non-bacterial serofibrinous pleural exudates unless absolutely necessary. Some men still adhere to this restriction. The intelligent use of indicated antibiotics in bacterial serofibrinous pleural effusions unquestionably prevents the development of a large number of empyemas. The satisfying experience with repeated antibiotic instillation and aspiration in indicated cases of bacterial serofibrinous exudates supports the continued use of this therapeutic and prophylactic practice. All bacterial serofibrinous effusions should be considered potential empyemas and treated accordingly.

As regards the treatment of tuberculous effusions the reader is referred to the section on tuberculosis.

LOUIS L. FRIEDMAN
SANDY B. CARTER

LÖFFLER'S SYNDROME

Löffler's syndrome is a nonspecific disease which is characterized by leukocytosis with eosinophilia and transient migratory infiltrations of the pulmonary tissue. It is generally considered to be an allergic pneumonitis and is most frequently associated with parasitic infestations of the intestinal tract. It has been observed in such conditions as ascariasis, amebiasis, trichinosis, infestation with *Strongyloides*, and in other parasitic diseases. Patients suffering from asthma, allergic rhinitis and urticaria also are known to develop this syndrome. The authors observed a case following smallpox immunization in a child. Since the disease is nonspecific the first step in the treatment of this condition

As a general rule, patients suffering from Löffler's syndrome are not particularly ill. Many of them remain ambulatory and, quite often the syndrome is recognized only accidentally in the course of a mass survey or other routine roentgen studies of the chest. With the exception of eliminating the responsible allergen, parasite or otherwise treatment of Löffler's syndrome is entirely

symptomatic Relief of local pulmonary symptoms such as cough and wheezing may be accomplished by the use of any of the available antihistaminic agents The drug of choice should be administered by systemic route at first If this fails aerosol antihistaminic therapy should be given a trial (see section on Chronic Bronchitis and Bronchiectasis) Evidence is accumulating which indicates that the antihistaminics are of real value in this condition

Bed rest is usually indicated Diet and fluid balance offer no problem because patients generally maintain their usual dietary habits during the illness For restlessness a suitable barbiturate or bromide preparation in required dosage should be prescribed liberally Analgesics and antipyretics are often required for general malaise and fever The symptoms are usually mild however and respond to 5 or 10 grain doses of acetyl salicylic acid at 3 to 4 hour intervals More severe symptoms in addition require $\frac{1}{4}$ (15 mg) or $\frac{1}{2}$ grain (30 mg) doses of codeine

Relief of aggravating or exhausting cough although infrequently a part of the clinical picture may require attention and treatment The most effective suppression of cough is obtained with anodynes (For treatment of cough consult section on Chronic Bronchitis and Bronchiectasis) Since there is no specific treatment for the pulmonary phase of this syndrome the symptoms are treated as they arise Those already mentioned are the most frequent However if other symptoms appear or if complications occur they are treated according to the specific symptom or complication

LOUIS L. FRIEDMAN
SANDY H. CARTER

EMPHYEMA

The successful treatment of pyothorax depends on the accomplishment of the following objectives sterilization and removal of the fluid and obliteration of the empyema cavity with subsequent re expansion of the lung The overwhelming majority of non tuberculous empyemas is due to the pneumococcus streptococcus and other bacteria with known susceptibility to available antibiotic agents Nonsurgical achievement of the enumerated objectives in the treatment

of these empyemas depends on the intelligent utilization of indicated antibiotics systemically and locally The method of treatment is generally the same as that recommended for antibiotic susceptible serofibrinous exudates There are a few important differences in technic The fluid must be aspirated completely each day and the pleural cavity washed with normal saline solution Re expansion of the lung should not be too rapid Loculated collections of pus may develop if re expansion occurs before sterilization of the pleural cavity is accomplished Once sterility of the pleural cavity is achieved re expansion of the lung should proceed without restriction It is imperative to follow the condition of the underlying lung with daily roentgen ray or fluoroscopic examinations throughout the duration of the treatment Additionally bacteriologic studies of the fluid must be performed each day These precautions will provide important information regarding endothorax and facilitate intelligent and safe management of each case Conservative management must be abandoned however if demonstrable evidence of clinical and bacteriologic improvement is not apparent after 3 or 4 days of treatment Failures are common in mixed putrid encapsulated and loculated empyemas Likewise empyemas which develop in spite of antibiotic therapy for the primary disease are also apt to resist conservative management

Empyemas associated with bronchopleural fistulas rarely respond to this form of therapy Poor results predominate the over all clinical results achieved in the treatment of chronic

pleural cavity is freed of infection Empyemas due to septic pulmonary infarction may also respond to conservative management only to recur each time an infected embolus lodges in the lungs Lasting cures in this instance will be achieved only after proper surgical treatment of the primary disease In the face of therapeutic failure conservative management of empyema should be abandoned The patient should be given the benefit of surgical treatment without undue delay Systemic and local administration of

antibiotic agents in indicated cases prior to surgical intervention will augment the therapeutic benefits of surgery. Postoperatively, the use of systemic and local antibiotic therapy is definitely indicated and unquestionably exerts a beneficial effect on the course of the disease.

It may be mentioned in passing that tuberculous empyemas rarely respond to conservative medical management. For a detailed discussion of this subject the reader should consult a satisfactory textbook dealing with the treatment of tuberculosis.

Supportive therapy in the conservative and surgical management of empyema is important. One should pay attention to the general condition of the patient. Maintenance of a satisfactory state of nutrition is an essential prerequisite to successful conservative or surgical treatment of empyema. Anemia, malnutrition, and avitaminosis are quite common. Anemia should be treated with repeated blood transfusions. The treatment of malnutrition and avitaminosis requires a nutritious diet high in carbohydrate, protein, and vitamin content. The diet should be supplemented with additional vitamins by mouth or parenterally. Occasionally, the use of any of the popular protein preparations is indicated. Other complications are treated as they arise.

Successful treatment of pyothorax requires the close co-operation of the internist and surgeon. Both must be open to suggestion and constructive criticism. If a feeling of mutual respect for each other's opinions prevails, patients with empyema will derive the full therapeutic benefits of co-operative medical and surgical management of their disease.

LOUIS L. FRIEDMAN

SANDY H. CARTER

PNEUMOTHORAX

The treatment of spontaneous pneumothorax depends entirely on its type and extent. Closed pneumothoraces usually require only symptomatic care. The amount of time required for the resorption of the gas depends on the size of the pneumothorax and the condition of the pleura. Usually, even the larger ones disappear within one month, and with the smaller ones it is only a matter of days. Indicated analgesics and sedatives

of choice may be used, respectively, for the control of pain and apprehension. Occasionally, the use of oxygen is warranted. Aspiration of some of the pleural gas is rarely necessary. Follow-up examinations are

spontaneous pneumothorax recurs frequently, it may be advisable to establish pleural symphysis. To accomplish this objective we feel that the introduction of various irritants into the pleural cavity may be of value. In this connection the use of the patient's own blood, 50 per cent dextrose solution and the insufflation of various powdered substances such as ordinary talc may be tried. Since the resulting aseptic pleuritis may be quite troublesome, this form of therapy should be reserved for the more serious types of pneumothoraces. The best treatment for the mild closed type is bed rest and symptomatic therapy.

Treatment of the open type of pneumothorax is generally similar to that of the closed variety. Paralysis of the hemidiaphragm on the affected side may be beneficial. Tension pneumothoraces require immediate heroic therapy. The use of a water trap is indicated in all these cases. To obtain the maximal benefit without delay, a 13 gauge needle should be used in the thorax. It should be introduced only far enough to permit the escape of the gas trapped in the pleural cavity. If it projects too far into the endothorax, additional tears in the pleura may result from coughing or any other activity which brings visceral pleura closer to the thoracic wall. The glass outlet tube should project no more than 1 cc. below the level of the water in order to obtain satisfactory results. When bubbling ceases, the rubber tubing may be occluded temporarily with a suitable clamp. After a satisfactory period of observation, if the patient manifests no further signs or symptoms of increasing pressure in the pleural cavity, the water trap may be disconnected. Before removing the needle from the chest, it is advisable to obtain a manometric reading of the intrapleural pressure. Since tension pneumothorax represents a real medical emergency, no time should be lost in reducing the intrapleural pressure. Sterile technique is desirable in accomplishing this result, but

on occasion there is no time for sterilizing the skin or for the production of a satisfactory local anesthesia. The introduction of the needle into the chest without delay is the paramount objective in the event of tension pneumothorax. When pneumothorax and pleural effusions coexist, therapeutic considerations are influenced chiefly by the nature of the fluid involved. The management

of the various types of pleural effusions is discussed in previous sections of this presentation.

In cases of spontaneous pneumothorax with a tuberculous etiology and demonstrable pulmonary tuberculosis, it is advisable to continue the pneumothorax if possible.

LOUIS L. FRIEDMAN

SANDY M. CARTER

DISEASES OF THE MEDIASTINUM

INFLAMMATION OF THE MEDIASTINUM

The treatment of acute mediastinitis depends entirely on the nature and extent of the inflammatory reaction in the mediastinum.

Specific therapy for the mediastinal disease is generally unnecessary since the process will automatically subside with effective treatment of the primary disease. The indicated therapeutic measures will depend entirely on the nature of the responsible primary infection. Even before the era of sulfa drugs and antibiotic agents the prognosis in this condition was favorable. The clinical management of nonsuppurative mediastinitis is entirely medical.

Acute Suppurative Mediastinitis. This is a serious condition, immediate recognition of its presence is the key to successful treatment since its course is fulminating and frequently fatal. Treatment is both medical and surgical. Large doses of a sulfa drug and indicated antibiotic agents are to be given. Since acute suppurative mediastinitis is most frequently the result of trauma, the simultaneous administration of penicillin, streptomycin, and the sulfonamide of choice is indicated. Treatment with chemotherapeutic drugs and antibiotic agents should precede surgical drainage and be continued postoperatively in large doses until the desired results are achieved. In order to save a life, the treatment of acute suppurative mediastinitis should be nothing short of heroic. A large number of cases follow accidental perforation of the esophagus during instrumentation. The bulk of these inflammations can be prevented by observing the necessary

precautions prior to, and during, instrumentation. An immediate gastrostomy should be performed following esophageal perforation which results from instrumentation or from intrinsic disease of the esophagus such as carcinoma. One is then confronted with the additional problem of maintaining a satisfactory state of nutrition. This objective is sometimes difficult to achieve in the presence of mediastinal suppuration. A well balanced, high caloric diet supplemented by large doses of vitamins is necessary.

Abscesses. Localized acute mediastinal abscesses should be treated in essentially the same manner as acute suppuration of the mediastinum. They usually result from extension of infections of the neck or from perforation of the esophagus.

Chronic mediastinal abscesses are generally due to tuberculosis, actinomycosis, blastomycosis, or syphilis. A tuberculous abscess usually results from involvement of the mediastinal nodes. The treatment of this condition is entirely medical unless complicated by draining sinuses. In this event surgical exploration may be indicated. Specific therapy with streptomycin or, preferably, dihydrostreptomycin, is indicated, especially in the presence of draining sinuses. Treatment with this antibiotic should be both systemic and local. The early results with this form of therapy are promising, but definite conclusions must await additional investigation. General symptomatic and supportive measures are important in the treatment of chronic tuberculous abscess of the mediastinum. Heliotherapy in the absence of pulmonary disease may be beneficial. Besides the general use of supplemental vitamins, large amounts of cod liver oil should be prescribed. Roentgen therapy is

Large doses of sulfa drugs and penicillin are indicated in the treatment of actinomycosis. Treatment is continued until the expected clinical results are achieved and maintained. Surgical excision of infected tissue and sinuses may be indicated and is frequently necessary to accomplish a permanent cure.

The medical management of blastomycotic mediastinal infection is hopeless. Treatment is entirely symptomatic. Excision of localized abscesses is the procedure of choice. The use of iodides and other medical measures are not even worth a therapeutic trial. Syphilis

therapy

The pain due to mediastinitis will respond to the usual symptomatic measures. The judicious use of narcotics is frequently necessary to alleviate the excruciating pain of localized and diffuse mediastinal inflammations.

LOUIS L. FRIEDMAN
SANDY B. CARTER

SPONTANEOUS MEDIASTINAL EMPHYSEMA

Spontaneous mediastinal emphysema is usually a self-limited process. In many instances the diagnosis is overlooked because of the paucity of significant symptoms or because of the physician's low index of suspicion. If the air manages to escape into the tissues of the neck, the clinical manifestations are likewise mild. Symptomatic treatment

will suffice in most instances. The control of pain and apprehension is the major consideration. Suitable narcotics or sedatives should be prescribed generously.

Larger mediastinal accumulations of air under pressure and those cases with an associated tension pneumothorax require more active and sometimes truly heroic treatment. In these instances, the clinical manifestation of pain, dyspnea, cyanosis and apprehension may reach alarming proportions. Unless immediate and energetic treatment is instituted, cardiac embarrassment, shock, or a fatal outcome may supervene quickly.

In the presence of an associated tension pneumothorax, effective relief of the alarming symptoms may be accomplished by establishing an avenue of escape for the air from the involved hemithorax. For a detailed discussion of this procedure the reader is referred to the section on Pneumothorax. In the event that the air is trapped and confined to the mediastinum, an artificial route of escape must likewise be provided. This is best accomplished by an adequate incision in the suprasternal notch. Aspiration of air from the mediastinum by needle is not recommended. The associated hazards are too numerous and the procedure requires real skill. Complete bed rest is indicated until all the symptoms and signs have subsided. Since mediastinal emphysema has a tendency to recur, drastic limitation of activity is indicated for several weeks following the original episode. In some cases relief of dyspnea may only require the use of oxygen therapy.

LOUIS L. FRIEDMAN
SANDY B. CARTER

FUNCTIONAL RESPIRATORY DISEASE

HYPERVENTILATION SYNDROME

The syndrome of hyperventilation occurs most frequently in psychoneurotic individuals. Certain organic diseases, however, may produce the same clinical picture through involuntary alteration of the normal depth and rhythmicity of respiration. Occasionally, it may be the result of vigorous exercise. As a rule, the syndrome does not follow ordinary physical exertion unless the subject is in poor condition or suffering from

fatigue. The hyperventilation syndrome identified with psychoneurotics is a self-induced clinical manifestation of emotional instability. Anxiety, apprehension, or general tenseness individually or in combination, are the responsible predisposing psychic and emotional factors. The altered respiratory pattern is characterized by overbreathing, either in depth or in frequency. As a result there is an excessive loss of CO₂, which results in alkalosis. The resulting symptoms of dizziness, paresthesia, tachycardia, tetany, and cyanosis

respond dramatically to a variety of simple therapeutic measures. The beneficial effects of symptomatic treatment of hyperventilation, however, are usually temporary. Permanent cures can be expected only after correction of the responsible organic disease or psychoneurotic basis. The nature of the underlying organic disease frequently precludes the possibility of lasting results. Such is the case when hyperventilation is the result of encephalitis lethargica and tumor of the floor of the fourth ventricle.

As previously indicated, lasting cures in these instances can be expected only after identification and correction of the responsible psychic factor. Identification of the psychic factor demands careful and prolonged psychiatric investigation. This study by the usual clinical methods commonly ends in failure. Narcoanalysis is generally necessary since the primary cause is frequently submerged in the subconscious. On occasion the responsible psychic factor is apparent to both physician and patient. Following accurate identification of the primary cause psychotherapy commonly fails to accomplish permanent or worthwhile clinical benefits. To date the available and tried psychotherapeutic measures including electric shock therapy, have produced generally disappointing results. Fainstaking attempts at education and readjustment of the patient commonly end in failure. Rationalization or removal of the provocative factor are equally difficult. Hyperventilation tends to recur with monotony and discouraging regularity even after the original psychic cause is eliminated. The inherent weakness in the emotional composition of these patients will provoke the abnormal response when they encounter ordinary problems of daily existence. They are unquestionably constitutionally inferior. The present psychotherapeutic approach to this group of patients is obviously inadequate and demands intensive study.

When the symptoms of hyperventilation occur they demand immediate action. Procrastination on the part of the physician and the patient's apprehension together contribute to the evolution of an alarming clinical

picture. Apprehension predisposes to continued overbreathing and vice versa. A state of shock may supervene unless the vicious cycle is broken. Inhalation of a 70 per cent oxygen and 30 per cent carbon dioxide mixture will afford prompt relief. Intravenous calcium produces equally dramatic but transient results. The mechanism by which calcium exerts its beneficial effects in this syndrome is not understood clearly. Ammonium chloride may be used in an attempt to prolong the effects of the more rapidly acting therapeutic measures. Sixty to 80 grams (4 to 5 gm) daily, in divided doses, are required. Clinical results with ammonium chloride are discouraging. The patient's symptoms regularly penetrate this weak symptomatic barrier after short periods of subjugation. Breath holding and rebreathing of expired air also are capable of producing rapid symptomatic relief. Demonstration of these palliative techniques in the presence of a patient's family or friends may have added therapeutic benefits. The indulgent concern of these people for the patient's welfare is a wonderful demonstration of devotion but only serves to multiply the patient's clinical symptoms. Psychoneurotics enjoy pity and attention. The prompt alleviation of the clinical symptoms with any of the above methods occasionally results in permanent cures. With the treatment as a starting point, a simple explanation of the mechanism involved in the production of the hyperventilation syndrome is helpful. Aviators and athletes who are innocent and accidental victims of this syndrome derive permanent benefits from this practice. The intelligent and co-operative patient will also benefit from a purposefully induced hyperventilation syndrome. With these patients the results achieved from in-

ably due to overactivity of the adrenal gland. The use of a sympatholytic drug such as ergotamine tartrate is indicated in this circumstance. Its use should be continued as long as there appears to be increased activity of the autonomic nervous system. The use

amounts may serve to break the vicious cycle and prevent the development of a permanent deep seated chain reaction. All in all, the treatment of the psychoneurotic patient who suffers from the syndrome of hyperventilation is at this time wholly inadequate and the results are correspondingly exasperating.

LOUIS L. FRIEDMAN
SANDY B. CARTER

HICCOUGH

Hiccough is due to a wide variety of causes which irritate either the afferent pathway to the centers in the upper cervical part of the spinal cord, the centers themselves, or their efferent pathway to the diaphragmatic and accessory muscles of respiration. In addition to the multitude of organic diseases which may cause hiccough (*singultus*), there may be a psychogenic origin. Treatment depends on the etiology. Regardless of the cause, persistent hiccough is commonly refractory to all forms of treatment. The frequent failure to control this annoying symptom has given birth to a panorama of therapeutic recommendations, perhaps second to none in the medical management of disease. The primary consideration in the treatment of hiccough should be identification of the responsible disease. After this objective is accomplished, successful treatment of the underlying disease will automatically abort the attack. Unfortunately, many of the responsible diseases are not remedial, and in other instances equal difficulty accompanies the effort to assign a specific cause for the development of singultus. At this point, the physician usually embarks on a trial and error attempt to control the attack symptomatically. Simple hiccough usually requires no therapy and its spontaneous termination rivals the suddenness which marks its onset. No doubt many of the recommended measures for the control of hiccough owe their birth directly to this fact. The therapeutic armamentarium unquestionably contains a large inventory of recommendations which owe their recorded success to a fortuitous application which accidentally coincided with spontaneous recovery from an attack. Failure to control persistent hiccough with all but a few of the recommended procedures substantiates this conclusion.

Hiccough which is associated with various gastric disorders may be treated by the administration of hydrochloric acid or gastric lavage. Treatment depends on the nature of the gastric disorder. When certain intestinal disorders such as acute pancreatitis, typhoid fever, acute appendicitis, obstruction or ileus are the cause of an attack, relief of the symptoms will result from successful treatment of these conditions. A cathartic or an enema

use of sedatives and the judicious administration of a narcotic drug may prove beneficial. Recovery frequently follows restful sleep induced by the necessary amount of intravenous sodium amytal.

Rebreathing, breath holding and the inhalation of a 90 per cent oxygen 10 per cent carbon dioxide mixture have a common mechanism and have proved successful in our experience. The use of indicated intravenous preparations to correct the electrolyte and water balance has a definite place in the management of those cases which complicate such conditions as diabetic coma and uremia.

Tracheal traction and cold water sometimes produce relief. Light anesthesia is an effective measure and deserves early consideration. Pressure applied to the phrenic nerve between the heads of the sternocleidomastoid muscle or application of ice bags or an ethyl chloride spray in the same area is frequently beneficial. Before surgical interruption of the phrenic nerve by crushing, division or avulsion is resorted to, all of the more conservative medical measures should be tried. Persistent hiccough, however, is occasionally associated with alarming symptoms which necessitate consideration of heroic measures. Relief of distention in the postoperative patient will frequently control an attack. There are innumerable other recommended measures for the symptomatic relief of hiccough. The bulk of these recommendations is cloaked in a penetrating and stifling aroma of quackery and does not merit repetition.

When hiccough is a manifestation of psy-

chogenic origin, the problem is even more difficult. Electric or insulin shock therapy may abort the attack. Application of psychotherapeutic measures commonly fails to produce permanent or even temporary relief. The discussion of the psychiatric aspects is essentially the same as that found in the

.

satisfactory

Quinine sulfate	grams xxiv
Tincture of valerian	dram i
Milk of asafetida	oz i
Water q s ad	oz iii

We have found that a teaspoonful of this horrible, but harmless, concoction every 4 hours, day and night, will abort an attack in most psychoneurotic individuals when other more popular measures have failed.

Hiccough which results from the presence of tumor masses in the mediastinum will be

controlled following surgical removal. Roentgen therapy may be used for radiosensitive masses. The treatment of refractory persistent hiccough requires a therapeutic trial with all of the recommended measures. Relief of the patient's symptoms and the physician's exasperation may come from the least expected source. Hiccough has a monotonous tendency to recur. Should this happen, the use of the previously effective measure is indicated immediately. This practice, however, is frequently attended by clinical failure. Consequently, the tedious procedure of therapeutic trial with the multitude of recommended measures is again necessary. The same treatment which relieved hiccough on one occasion will fail on subsequent occasions. Conversely, previous failure with a therapeutic measure does not preclude the possibility of future success.

LOUIS L. FRIEDMAN
SANDY B. CARTER

pressure in the systemic circuit is higher than that in the pulmonary circuit. Under such circumstances some of the aerated blood is sent a second time to the lungs. Cyanosis is absent. If, however, there is some obstruction to the outflow of blood from the right side of the heart, blood may be shunted from the venous to the arterial side. If a sufficient amount of blood is thus shunted, cyanosis results. There are also a number of anomalies involving the heart or great vessels in which no shunt exists. Hence Dr. Abbott established the following classification:

- I Cases of arterial venous shunt
- II Cases of venous arterial shunt
- III Cases in which there is an absence of shunt

It is an interesting fact that surgery has been used successfully for cardiovascular defects in each of these three groups.

Surgical Treatment PATENT DUCTUS ARTERIOSUS. In 1939 Gross and Hubbard reported the first successful ligation of a patent ductus arteriosus. Since the pioneer work of Gross many other surgeons have entered the field, so that at present the operation is quite well standardized and in expert hands carries a low mortality. On one point the surgeons are not yet completely agreed, and that is whether the ductus should be ligated or severed. The objections to ligation are that a good deal of foreign material is left in the chest and that in a small percentage of cases recanalization of the ductus occurs. The objection to severing the ductus is the danger of uncontrollable hemorrhage. At the Children's Memorial Hospital Dr. W. J. Potts has, at the time of writing, operated on 72 patients with patent ductus. In the first 20 ligation was done. The remaining 52 have all been severed. Because of a special ductus clamp which he has devised, he feels that the danger of hemorrhage is practically eliminated. There has been no fatality or serious complication in either group.

The ductus arteriosus is normally open during fetal life. It arises from the pulmonary artery near the bifurcation of the right and left branches and enters the aorta just distal to the origin of the left subclavian artery. In normal cases the ductus closes within the first 2 or 3 months of life. Why in certain individuals the ductus fails to close, and even becomes enormously enlarged, is not known.

In uncomplicated cases of patent ductus, blood passes from the aorta to the pulmonary side. Inasmuch as the shunt is arterial venous, cyanosis is absent. It has been shown that in cases of patent ductus the amount of blood shunted may be as much as 70 per cent of the blood leaving the left ventricle. It is obvious that under such circumstances the work of both ventricles is increased.

The symptoms and signs are poor appetite, underweight, easy fatigability, cardiac enlargement, a machinery murmur present at the base of the heart, and a capillary pulse. The diastolic blood pressure is low. In many instances the roentgen film shows

the typical physical signs of a patent ductus but who manifest no evidence of cardiac overwork. It is a debated question whether these children should be submitted to operation. There are arguments in favor of operation in these circumstances. Bacterial endarteritis is less likely once the ductus has been closed. The operation is safer and easier in children, hence if surgery is contemplated it should not be too long delayed. It is essential that precautions be taken to eliminate the possibility of associated anomalies which might contraindicate closure of the ductus. Pulmonary stenosis is an example of such a lesion. Therefore, any degree of cyanosis even on exercise, appreciably decreased oxygen saturation of the arterial blood, or right heart strain in the electrocardiogram should make one wary as to the advisability of closing the ductus.

The good effects of operation in the typical case are almost immediately apparent. The appetite is improved, there is a gratifying gain in weight, and exercise tolerance is increased. Following operation the heart is less tumultuous, the pulse pressure is normal, and the heart shows, after some months, a definite decrease in size.

CONGENITAL PULMONARY STENOSIS. Con-

... of the more
t rarely
and most
frequently in conjunction with defect of the ventricular septum, dextroposition of the aorta, and hypertrophy of the right ventricle. This syndrome is known as the tetralogy of

Fallot In this condition there is an inadequate supply of blood to the lungs because of the pulmonary stenosis. Because the aorta overrides the ventricular septal defect some of the blood from the right ventricle is pumped directly into the aorta. Hence a portion of the venous blood passes directly into the arterial circuit without traversing the

the lungs and that by the same token the pulmonary flow is so small that insufficient blood reaches the lungs for aeration. Cyan

creased flow of blood to the lungs would relieve cyanosis to some extent and increase the child's exercise tolerance and general well being. This was accomplished by doing an end to side anastomosis between one of the branches arising from the aortic arch (usually the subclavian artery) and the right or left pulmonary artery. The results of this operation were better than they had dared to hope. Children who had been extremely cyanotic, markedly underweight, unhappy and fretful and unable to walk more than a few steps were transformed into children whose cyanosis was greatly relieved, who were able to play almost as do normal children and who showed a profound improvement in their general outlook on life. In 1946 Potts, Smith and Gibson reported a modification of the Blalock operation whereby a direct anastomosis was made between the aorta and the pulmonary artery. This was made possible by the use of a clamp which encircled the aorta and merely pinched off a lip of the vessel, thus allowing blood to course through the aorta while the anastomosis was being performed. The principle of the operation varies in no way from that of the Blalock operation.

Diagnosis of the tetralogy of Fallot rests upon symptoms, physical examination, roentgenographic and fluoroscopic examination, the electrocardiogram and oxygen studies of the peripheral blood. In doubtful cases cardiac catheterization and angiocardiology may be helpful in arriving at a diagnosis.

There are certain general principles which

should be observed in performing the Blalock or Potts-Smith operation for the relief of congenital pulmonary stenosis. These patients are in serious condition and therefore the surgical risk is great. Inasmuch as the operative risk is greater in young infants, operation should be deferred until the patient is 1 or 2 years old when the condition is sufficiently benign to permit waiting. Great care must be taken to see that the patient is free from respiratory or other infection at the time of operation. Penicillin should be given for 24 hours prior to operation and for several days following operation. Expert anesthesia is just as important as expert surgery. Inasmuch as the chest is open, one lung partially collapsed and one pulmonary artery occluded during the anastomosis, it goes without saying that the margin of safety is extremely small. Dr. William O. McQuiston, who has been the anesthesiologist in practically all of the "blue baby" operations carried out at the Children's Memorial Hospital, has regularly employed an endotracheal tube and cyclopropane with a high percentage of oxygen. This has been the usual anesthetic.

It can be readily understood that so extensive a surgical procedure carried out in an infant or child so seriously handicapped will carry an appreciable mortality. In a series of 189 cases of congenital pulmonary stenosis operated on by Dr. W. J. Potts and his associates, the overall mortality where anastomosis was completed was 9.3 per cent. The highest mortality occurred in babies under 1 year of age. In fact, in all patients between the ages of 3 and 16 years, the mortality was only 3.8 per cent.

Regardless of the poor condition of any patient, operation is obligatory if one can be certain of the diagnosis. Some of the patients who seemed utterly unable to stand the shock of the operation came through the procedure in splendid shape and showed truly amazing postoperative benefit.

The outlook without operation is so poor that the surgical risk is well justified.

COARCTATION OF THE AORTA The adult type of coarctation of the aorta consists of a localized constriction of the aorta usually at a point just distal to the origin of the left subclavian artery.

In 1945 Crafoord and Nylin reported the

first successful operation for this condition. This operation consisted in excising the narrowed portion of the aorta and doing an end to end anastomosis. This technically difficult operation has proved to be feasible in lowering the excessive blood pressure in the upper portion of the body and supplying a more effective circulation to the lower portion. In the majority of instances patients with coarctation of the aorta are free of symptoms during childhood and have a normal exercise tolerance. It has been quite clearly shown, however, that the majority meet with disaster before they have lived out a normal span of life. The chief causes of death are bacterial endarteritis, rupture of the aorta, cerebral vascular accidents and heart failure.

It would seem therefore, in cases where the hypertension in the arms is at all extreme, that the possible danger from these complications would justify the surgical risk involved. At the present time it is fairly well accepted that the operation is both easier and of greater benefit in childhood. The optimal time for operation is between the sixth and 15th years.

DOUBLE AORTIC ARCH In 1945 Gross reported the first successful operation for the relief of symptoms due to a double aortic arch. In this condition both the right and left fourth branchial arches persist. The ascending aorta divides into two portions, the anterior portion passing in front of the trachea and esophagus, while the posterior portion passes behind them. These two portions of the aorta unite to form the descending aorta. It is thus seen that the trachea and esophagus are completely encircled by a vascular ring. In many instances the trachea and esophagus are so compressed that serious and even fatal symptoms may result. The symptoms are those which result from interference with the airway—a wheeze, a brassy cough, difficult respiration and frequent respiratory infections. Less often dysphagia is also present, particularly on the effort to swallow solid food. The diagnosis is made by noting on roentgenographic or fluoroscopic examination a compression of the barium filled esophagus at the level of the aortic arch, and by a similar compression of the trachea as visualized by direct bronchoscopy or the use of lipiodol.

The surgical procedure consists in sever-

ing one segment of the vascular ring. By this means the constriction of the trachea and esophagus is relieved. The operation should be performed as soon as the diagnosis is made inasmuch as the patient is in constant danger both from obstructive symptoms and respiratory infections.

Medical Treatment In spite of the great contribution of recent surgery in congenital cardiovascular anomalies there are still many children with types of anomalies which, in the present state of our knowledge, cannot be relieved by surgical means.

For this group of patients too often neglected, it is our obligation to plan a regimen which will give them as satisfactory a life as circumstances will permit. Many of these patients suffer from so mild a form of congenital heart disease that they can enter into the usual activities of childhood. Even in the more severe cases, especially those which are cyanotic, it is usually not necessary to restrict their exercise. It is difficult for the parent, and sometimes for the family physician, to accept this point of view. Yet it must be remembered that these children have grown up with their handicap and from their first attempts at exercise they have learned how much they are able to do. Hence they will stop of their own accord when they become tired. They should not be placed in gymnasium classes or in competitive games if experience has shown that they become

ould be
normal
ed out.

Every effort should be made to avoid respiratory or other infections. Tonsillectomy and tooth extraction should be done when indicated. Because of the ever present danger of bacterial endocarditis, the sulfonamides or penicillin should be administered prior to operation and for a few days thereafter. Other surgical procedures should be carried out when indicated. One is constantly amazed to see how well the "blue babies" tolerate the long and strenuous surgical procedure necessary for their relief. This furnishes ample evidence that the usual major operation will be well tolerated.

One of the dangers to which the cyanotic child is exposed is that of cerebral thrombosis. This danger is increased by dehydration.

Hence an adequate fluid intake should be scrupulously maintained especially in warm weather or in the presence of fever. Upon the appearance of the first signs of cerebral thrombosis, venesection and heparin are indicated together with intravenous fluids until the patient is able to take fluids by mouth.

dose hourly as necessary to maintain the clotting time at 20 or 30 minutes.

Paroxysmal dyspnea is a frequent occurrence in infants suffering from severe anoxemia. The infant becomes limp, the breathing is difficult, the cyanosis becomes markedly increased and unconsciousness may supervene. He should be immediately placed in

face down with his legs drawn up under him.

Subacute bacterial endocarditis is a constant menace to the child with a congenital cardiac defect. Before the days of modern chemotherapy it was the most feared complication. With the advent of penicillin the dangers resulting from this complication have been greatly reduced.

The management of heart failure in congenital heart disease is similar to that in acquired heart disease. Complete bed rest is indicated. Oxygen is helpful. Digitalis should be administered in accordance with the usual rules. One cat unit for each 10 lbs of the patient's weight is usually considered the average digitalizing dose if given within a 24 hour period. One half the digitalizing dose may be given initially followed by the remaining half in divided doses at intervals of 6 hours. In urgent cases the digitalis may be administered intramuscularly. The daily maintenance dose of digitalis is estimated to be about one tenth of the amount necessary to produce digitalization. It should be emphasized however that there is extreme variation in the tolerance of children to digitalis. I have seen many instances where more than twice the usual dose was necessary to produce a digitalis effect and others where the usual dose quickly induced digitalis intoxication.

In the infant or young child vomiting is the chief symptom of overdosage of digitalis.

Careful and frequent auscultation of the heart is essential to detect disturbances of rhythm. Frequent electrocardiograms may serve to show the approach of digitalis intoxication before other symptoms or signs are manifest.

genital heart disease. The fact that he has a relatively incapacitating lesion does not necessarily condemn him to an early death or a useless unhappy life. The famous musician with tetralogy of Fallot who lived to the age of 60 years should convince us that we have not only the right but the obligation to assume a hopeful attitude in our management of these patients. Occupations should be planned which lie within their physical possibilities. They must be encouraged to seek a responsible satisfying life rather than using their physical handicap as an excuse for leading an aimless existence.

STANLEY GIBSON

REFERENCES

- Pulmonary Stenosis or Pulmonary Atresia
JAMA 128 189 1945
Crafoord, C. and Nylin, G. Congenital Coarctation of Aorta and Its Surgical Treatment J Thoracic Surg 14 347 1945
Gross, R. E. Surgical Relief for Tracheal Obstruction from Vascular Ring New England J Med 233 586 1945
Gross, R. E. and Hubbard, J. P. Surgical Ligation
1946
Taussig, H. B. Congenital Malformations of the Heart New York: The Commonwealth Fund, 1947

THE CARDIAC ARRHYTHMIAS

In considering the treatment of any cardiac arrhythmia it must always be kept in mind that the abnormal rhythm is not a disease of itself. It is a symptom either of definite cardiac damage or of some extrinsic factor which influences the heart mechanism. This

must not be forgotten no matter how successful the treatment of the arrhythmia may be. This sounds like an unnecessary commonplace, but it is frequently forgotten, especially when the rhythm remains normal after a lapse of time.

Paroxysmal Auricular Tachycardia Paroxysmal auricular tachycardia is one of the least serious of the cardiac arrhythmias, so far as health or life is concerned. But it is one of the most troublesome and inconveniencing problems for the patient, and troublesome to the physician because he has at his hand no one specific remedy which might be uniformly helpful.

The immediate attack of paroxysmal tachycardia does not require any treatment of itself when it is of short duration and when it produces no uncomfortable symptoms. Attacks which last long enough to cause uncomfortable symptoms or which are frequently repeated will demand attention.

In the case of attacks of shorter duration, the patient may continue with what he is doing, and the symptoms may disappear, or he may stop and stand erect. Usually, however, the attack will stop more promptly if the patient sits down until it is over, or, when possible, assumes a recumbent position.

There is an infinite variety of simple methods for stopping an attack, such as sitting in a chair and bending forward, with the head between the knees, or taking a deep breath and holding it. It may be stopped by taking a deep breath and coughing, or inhaling with glottis closed or by lying down with the feet higher than the head or by lying on the back with the arms outstretched and breathing deeply. Forcing a belch may stop the attack. Putting the finger in the mouth and imitating a gag reflex or even emesis may be beneficial.

Methods of recourse may be had to carotid sinus stimulation. This is effective in most cases. The carotid sinus is located by the fingers at the level of the carotid artery and the thyroid cartilage. It is better to use all four fingers in order to cover a wider area and be sure of finding the sinus. Pressure should be firm over the artery, compressing it between the palpating finger and the vertebral column for a few seconds, changing

the position of the fingers if there is no response. A massaging motion may be used. Which side is stimulated makes little difference and usually the response is prompt. Both sides should not be stimulated simultaneously. Stimulation may be accomplished more readily by standing behind the patient when he is in a sitting position. However, in some cases, it may be more effective when the patient is prone in bed. The response can usually be felt by the palpating finger. Unless the attack has lasted long enough to cause evidence of cardiac decompensation the patient is usually aware of the change in rhythm at once. It is a simple procedure, and there are many instances in which someone in the family may be instructed in its use. Some patients can do it themselves.

Pressure upon the eyeball may cause a similar reflex. It is unpleasant to some patients and usually not as effective as other methods. Nevertheless, there are a few instances where it is effective when carotid sinus pressure is not.

Syrup of ipecac is often effective in stopping the paroxysms. It is given in doses of 1 to 2 drams (4 to 8 cc) repeated in one hour, if necessary. Emesis may result, and if so the medication may be more effective.

Quinidine sulfate may be used orally in attacks resistant to other treatment. It can be given in 3 grain (0.2 gm) capsules every 2 hours for six to eight doses. If there is an idiosyncrasy, it should reveal itself in the first one or two doses, and the drug is to be stopped if there is any evidence of quinidine poisoning, such as tinnitus, dizziness, nausea, vomiting, diarrhea, or urticaria. It may be continued for several days. Quinidine may be used parenterally if necessary. Not more than 7½ grains (0.5 gm) should be given slowly by the intravenous route, and administration is to be stopped at once when the normal mechanism returns. It can also be given intramuscularly, 7½ grains (0.5 gm) every 2 hours, up to three to five doses if necessary. Dihydrochloride quinidine, 0.3 gm, may be used if quinidine is not available.

Acetyl beta methylcholine may be used if it is administered carefully, and may be adequate when other means fail. It should be remembered that the sun shines equally on the just and the unjust, and evidence of vagal stimulation may occur elsewhere, which may

be not only undesirable but definitely alarming. Doses of $\frac{1}{4}$ to $\frac{3}{4}$ gram (10 to 40 mg) may be used intramuscularly, with a constrictor applied proximally, released at intervals, allowing a gradual absorption or a rapid termination of absorption should symptoms appear. A syringe loaded with atropine, $\frac{1}{100}$ gram (0.6 mg) should be immediately available. The propriety of the use of acetyl beta methylcholine is doubtful.

Neostigmine, $\frac{1}{50}$ grain (0.4 mg) intramuscularly, has been used successfully to abort the attacks, or prostigmine bromide, 15 mg, may be used by mouth two or three times a day to prevent the attacks.

Sedatives, such as bromides or one of the more rapid acting barbiturates, i.e., 0.1 gm of secenal, are always of some use, and may aid a great deal in the efficacy of the more simple measures. Morphine sulfate $\frac{1}{4}$ grain (15 mg) is sometimes of value, especially if it tends to bring on nausea, but the danger of its being habit forming if used repeatedly should be kept in mind. Carotid sinus pressure may be more effectual after a sedative.

Potassium and/or magnesium salts are best reserved for hospital practice.

In every case of paroxysmal tachycardia, as in all of the arrhythmias, every effort should be made to determine what is the underlying cause or what is the trigger mechanism. Our efforts are often fruitless but are not as hopeless as is usually assumed.

There are probably more cases of paroxysmal tachycardia which are migraine equivalents than are recognized, and a careful personal family history should be taken

cases are migraine equivalents. In some instances desensitization is successful. Allergy may be a factor, even though there is not a

lent prescription consisting of tincture of belladonna in elixir of phenobarbital, may be effective.

Tr belladonna	80
Elixir of phenobarbital q s ad	300
Sig —1 teaspoonful 3 times daily before meals	

An accompanying spastic constipation should be treated without cathartics. Strychnine may be of value. An achlorhydria must be considered. Every possible factor should be unearthed such as the influence of fatigue, overwork, tobacco, liquor, etc. Occasionally an attack will follow sudden exertion.

In the instance of repeated attacks quinidine, 3 grains (0.2 gm) taken three or four times a day, may be used. There are some cases in which the heart is not normal and in which there is some residuum of rheumatic carditis. In some of these digitalis is of advantage, as it is in some other cases. It should be used in small, carefully observed doses. Occasionally its use will induce auricular fibrillation. In this event it should be discontinued at once and the rhythm will return to normal. However there are instances of frequently repeated paroxysms of tachycardia in which an auricular fibrillation may render management easier. The auricular fibrillation can always be controlled by digitalis.

Paroxysmal Ventricular Tachycardia
Paroxysmal ventricular tachycardia must always be carefully differentiated from other tachycardias. It should never be treated simply as a tachycardia. With only rare exceptions it is of grave import, and ventricular fibrillation and death are only one step removed. Treatment should be directed to the underlying cardiac disorder, of which the tachycardia is but one expression.

The most frequent cause is myocardial infarction which must be treated promptly as such. Coronary occlusion should be suspected in every case of paroxysmal ventricular tachycardia. There will be some cases consequent upon coronary insufficiency, without actual occlusion or infarct, in which there will be short episodes of paroxysmal ventricular tachycardia which appear after effort or emotion, or apparently spontaneously. Such cases may be treated with coronary vasodilator drugs, as aminophylline, 72

bin determinations can be made.

Overdosage with digitalis is a frequent cause of ventricular tachycardia. In such cases the digitalis should be stopped at once. If edema is present, diuretics should not be

used as the return of digitalis laden edema fluid into the circulation may bring on a fatal digitalis intoxication

The question as to the use of quinidine is not as simple as it sounds. It does depress the irritability of the ventricular muscle but at the same time it depresses every other function of heart muscle. Its use may be of benefit in some cases and in others it is harmful. If a case of coronary occlusion is promptly and adequately cared for there will be little indication for the use of quinidine. Sporadic cases of ventricular tachycardia are best treated by means of coronary vasodilator drugs such as aminophylline 7½ grains (0.5 gm) intramuscularly.

If quinidine is used care must be taken not to produce any untoward reaction. It is best to give 3 grains (0.2 gm) every 2 to 3 hours. If any toxic symptoms appear such as nausea, diarrhea or tinnitus the drug should be stopped.

In the absence of any signs of idiosyncrasy or toxicity the drug may be continued every 2 hours night and day and if necessary the dose may be increased to 6 grains (0.4 gm) every 2 hours until the tachycardia disappears.

There are doubtless occasional cases of paroxysmal ventricular tachycardia which occur without any apparent underlying pathology. It is best to assume that there is some cause which has escaped attention and diagnosis.

Auricular Fibrillation. Auricular fibrillation almost invariably presupposes some degree of cardiac damage. There are some cases, however, associated with a toxic thyroid in which the heart returns spontaneously to a normal mechanism after a normal metabolic rate is restored. In some of these cases the amount of permanent cardiac damage may be slight.

There are cases of paroxysmal fibrillation in which the heart is apparently normal. Some of these are consequent on some extra cardiac stimulus, as a hiatus hernia or cholelithiasis. An occasional case of fibrillation may occur as an allergic response. Digitalis may induce fibrillation in some hearts in which there was previously a normal mechanism. In some of these patients it is a question whether or not there is some degree of predisposing cardiac damage.

Attacks of paroxysmal fibrillation are best treated with rest and mild sedatives such as phenobarbital ½ grain (30 mg) three times daily. If a provocative condition is found, it should be cared for. Digitalis is not indicated if the attack is purely paroxysmal as it may serve to perpetuate the condition. If the paroxysmal attack persists, quinidine may be used in a dose of 3 grains (0.2 gm) every 2 to 3 hours.

Auricular fibrillation in which the heart rate is normal and in which there is no dyspnea or other evidence of passive congestion does not demand treatment. It is the rapid rate and not the fibrillation which constitutes the mechanical disadvantage.

Auricular fibrillation which has become permanent and in which the rate is rapid, always demands treatment. If dyspnea and passive congestion are not already present, they soon will be if the rapid rate is not adequately controlled. For treatment, digitalis carefully administered and carefully watched is an almost ideal drug. There are few therapeutic measures in medical practice which are as efficient or as satisfactory.

During the first few days or until there is little or no evidence of passive congestion, bed rest should usually be enforced. The degree and extent of the bed rest will, of course, depend primarily on the cardiac condition.

The dosage and the rate of administration should be guided by observation of the clinical results only and not by any rule or formula, although these may be useful if not taken too literally. There is rarely need for precipitate haste. The patient's interests will usually be adequately served if the powdered leaf is administered in doses of 3 grains (0.2 gm) or 1½ grains (0.1 gm) of the standard U.S.P. pills every 4 hours or four times daily until there is clinical evidence of adequate dosage as evidenced by decrease in pulse rate, decrease of dyspnea and cyanosis and increase in urinary output. No attempt should be made to follow any rule as to pulse rate or pulse deficit. The full dosage should not necessarily be kept up until all evidence of passive congestion has disappeared. The residual edema must necessarily disappear with the increased cardiac output and increased blood flow through the kidneys. If it does not, other factors must be investigated.

gated, as kidney function, salt intake, plasma proteins, etc

Once the optimal clinical level of digitalis has been reached, a daily dosage just sufficient to maintain this level should be given. For this there is also no rule, and there are wide variations in the amount of digitalis

much. The effect of the dosage should be watched, and carefully adjusted as necessary. Often a dose every second day is sufficient, but even this may be too much and may be toxic. Whatever may be the advantage of digitalis glycosides, a constant, adequate level is more readily maintained with the more slowly absorbed and more slowly excreted, whole leaf preparation.

Patients may be maintained for years in a satisfactory state of health as far as the fibrillation itself is concerned. Untoward changes may occur because of intrinsic cardiac conditions, and they occur frequently

dosage often closely approximate one another. Hope observed in 1834 that digitalis increases blood coagulability. Intravascular thromboses may be induced (de Takats, Trump, and Gilbert). Digitalis also acts as a coronary vasoconstrictor in the higher levels of dosage, and often in levels not so high (Gilbert and Fenn). Because of this, it has the additional disadvantage of inducing degenerative changes in the heart muscle (Kyser, Ginsberg, and Gilbert). These changes can be obviated in large part by the daily administration of coronary vasodilator drugs such as aminophylline or theobromine calcium salicylate (theocalcin). Quite apart from obviating the effects of

also taken, a tablet after each meal.

Each patient should be taught the use of digitalis, just as diabetics are taught the use of insulin. They must learn the danger signals, such as coupled pulse. They should be taught to keep the pulse rate at its optimal

level, and to vary the digitalis dosage accordingly. They soon learn to keep the dos-

can learn to take the apical pulse rate. No matter how well this is done, the patient should be checked by the physician at regular intervals, this should include observation

tion of action and as to potency, they have the great advantage of more rapid absorption, and are adapted to parenteral use. The physician who elects to use them should limit himself to one preparation with whose clinical use he is perfectly familiar.

Digitoxin is perhaps the most useful of

had some form of digitalis. In addition to this, there are wide individual variations. Parenteral administration is useful in cases where a high degree of passive congestion has resulted in nausea.

Quinidine is of limited value. Its use should be reserved for those cases of fibrillation that show little or no evidence of cardiac damage. In cases of auricular fibrillation with a toxic thyroid, it is frequently of great value after the metabolic rate has returned to normal. In prescribing quinidine a test dose of 3 grains (0.2 gm) three times daily should be tried. If no signs of toxicity, such as nausea, diarrhea or ringing in the ears, occur the dose may be increased to 0.2 gm every 2 to 4 hours until normal rhythm is established.

In cases of actual cardiac damage, even if a normal mechanism has been restored by quinidine, the duration of the quinidine effect will usually be brief, and the clinical course no better, if as good, as it will be with digitalis. Quinidine should never be

used if there is the slightest chance of an embolism being released when a normal mechanism is restored and the auricles again function normally

Auricular Flutter. While auricular flutter has some of the aspects of a paroxysmal tachycardia, accompanied by some degree of heart block, it is quite different in character. It is almost invariably associated with some type of cardiac disease, as rheumatic carditis, coronary artery disease, or cardiac syphilis, or may be seen as one of the consequences of thyrotoxicosis or hypertension. Rarely is it an early symptom of coronary occlusion. It may occur in an apparently normal heart.

Treatment of the short paroxysmal attacks should be directed toward the primary cardiac condition as well as any known precipitating factors such as fatigue, overexertion, nervous factors, or indiscretions in food or drink. In attacks of short duration no treatment of the immediate attack may be necessary. Occasionally a paroxysm may yield to carotid sinus pressure.

When the abnormal rhythm persists it will almost invariably respond favorably to digitalis therapy, either in one way or another. The powdered leaf in 3 grain dosage (0.2 gm.), or the standard USP pills, 1½ grain (0.1 gm.), may be given three or four times a day until some evidences of digitalis effect occurs. The rhythm may change to an auricular fibrillation. If digitalis administration is discontinued at this point, the rhythm may revert to normal and no further treatment may be necessary, aside from rest and possibly small doses of quinidine for a few days. In cases in which there is any reason to suspect an active intracardiac process with mural thrombi, the possibility of embolism must always be kept in mind with a return to normal rhythm.

If auricular fibrillation persists, digitalis should be continued in doses sufficient to maintain an optimal pulse rate. If the auricular flutter persists but with a higher degree of block, maintenance dosage of digitalis should also be continued to keep the heart rate at an approximate normal.

In some cases, in which a high degree of passive congestion is inducing serious symptoms, it may be advisable to secure a more prompt digitalis effect by means of one of the more rapidly absorbed and more rapidly

acting digitalis glycosides, either orally or parenterally.

If a normal mechanism is not restored by digitalis quinidine may be tried, as in auricular fibrillation. It may sometimes be successful when digitalis has failed. When a normal rhythm has been restored by either method it is usually best to administer small doses of quinidine, 3 grains (0.2 gm.), three or four times daily, for a few days.

Treatment of the arrhythmia itself is indicated. This does not mean that the condition should be blandly ignored. Every effort should be made to assure the patient that the condition is not serious.

A careful history should be taken to determine the possibility of any etiologic factor which could be corrected. Fatigue predisposes to attacks as do emotional disturbances and excessive smoking. Gastrointestinal factors such as indigestible meals or meals eaten too hurriedly may produce extra

responsible for premature ventricular contractions when the dosage has passed a certain point.

If medication must be given because of the patient's reaction to the occurrence of these ectopic beats in spite of reassurance, quinidine sulfate, 3 grains (0.2 gm.) three times a day may be used. Effervescent triple bromides 15 grains (1.0 gm.), two or three times a day may be effective. A small dose of phenobarbital ½ gram (30 mg.) night and morning may help. Or strychnine sulfate, 100 grains three times a day, after meals is helpful. If potassium salts are used, the possibilities of harmful effects must be considered.

Heart Block. Heart block, either partial

the heart block is based on intrinsic anatomic changes, these are usually of an irreversible nature, as when the block follows invasion of the conducting pathways by inflammatory processes or when it is consequent upon a congenital defect. When it

is due to coronary changes, improvement may follow the use of the coronary vasodilator drug, if the fibrosis has not progressed too far. Diphtheria rarely causes a permanent heart block. Syphilis may cause heart block which may yield to careful antiluetic treatment. Cardiac contusions, as steering wheel accidents, may cause heart block. Any case of cardiac contusion should have an electrocardiogram taken at once. If there are changes the patient should be kept in bed for from 4 to 6 weeks. Fatal results of cardiac

usual cases resulting from vagus stimulation, atropine is not useful.

Constant daily use of a coronary vasodilator drug such as aminophylline or theocaine over long periods of time is rational and may serve to maintain the pulse rate at higher levels and obviate the syncopal attacks. When the attacks occur at short intervals, epinephrine solution 1:10,000, in doses of 1/2 cc. may be used to increase the pulse rate because

it is more slowly absorbed and when the effect begins to wear off it may be renewed by massaging the site of the injection. Only two or three injections every 24 hours may be needed. When needs are less urgent, ephedrine sulfate may be used, in doses of 1/4 grain (8 mg.) to 1/2 grain (30 mg.) as needed. As small a dose as possible should be used because of its unpleasant effect in increasing nervousness. Barium chloride has been used but it is not especially effective and is of doubtful propriety. For emergency treatment during an attack in which death seems imminent, intracardiac injections of epinephrine solution, 0.25 to 1 cc., may be lifesaving and may help after apparent death. Occasionally patients may live for years after such an episode.

NEWELL C. GILBERT

REFERENCES

Gilbert N. C., and Fenn G. K. Effect of Digitalis on Coronary Flow. *Am J Med Sci* 66: 600, 1923.

1946
deTakats G., Trump, R. A. and Gilbert N. C. Effect of Digitalis on Clotting Mechanism. *JAMA* 125: 840, 1944.

Thomas W. A., and Butler S. Treatment of Migraine by Intravenous Histamine. *Am J Med Sci* 39, 1946.

Thomas W. A. and Post M. C. D. *Am J Med Sci* 39, 1946.

W.

1946, and 1947, 1948.

NEUROCIRCULATORY ASTHENIA OR EFFORT SYNDROME

Since Sir Thomas Lewis first described neurocirculatory asthenia, or as he more aptly termed it, the "effort syndrome," the basic

the course of rheumatic fever or diphtheria, or some other acute infection as in cases diagnosed as influenza. The block will usually disappear with the subsidence of the acute infection. Temporary heart block may result from digitalis or, more rarely, from quinidine. Intensive roentgen therapy directed over the heart may cause a heart block which may or may not disappear with time.

Vagus stimulation from any one of several extrinsic sources may also cause heart block. This may occur in cases of esophageal diverticula, hiatus hernia, cholelithiasis, or pleural scars from roentgen therapy. Allergy to certain foods may cause a temporary heart block. Pulmonary embolism may be the etiologic factor (Kauffmann), most of these cases may be obviated by attention to the causative factor.

Patients showing passive congestion and in whom there is heart block may be helped by digitalis in small doses. Careful observation and great care must be exercised so that the condition will not be made worse, or a complete block induced, with possibly a Stokes-Adams syndrome. When complete heart block is associated with Stokes-Adams syndrome, watchful care and treatment are imperative, keeping the patient in an environment where a sudden attack would not bring serious results. Care must also be exercised in regard to the patient's activities. Overexertion or fatigue may predispose to attacks. Sources of vagus stimulation should be investigated. One case following vagus stimulation, which resulted from pleural scars due to roentgen therapy, was free from attacks with daily doses of belladonna and phenobarbital. Except in these rather un-

structure has been considerably altered. A great deal has been written lately, indicating that this is a psychiatric problem. In this section, however, the subject will be treated as it concerns the practitioner of internal medicine.

It will help greatly in our therapy of this condition if we turn to Sir Thomas Lewis' original concept of a group of symptoms consequent on effort. The effort syndrome is not a disease and its diagnosis requires that the heart and circulatory system be anatomically normal. Neither is it a psychiatric entity, in spite of many suggestive symptoms. The symptoms and physical signs are those which would appear in any of us on exertion, but in this condition they appear with a minimum of exertion and are greatly exaggerated. There is a lowered threshold to autonomic stimuli and of over-response to those stimuli. Some of us might exhibit not only the same physical symptoms, but the same psychologic symptoms as well with sufficient physical or nervous trauma. The increased incidence of this syndrome in war times is due to the fact that there is an increase in physical and nervous trauma.

Our therapy will be clarified if we divide our patients exhibiting symptoms of the effort syndrome into five groups, much as Sir Thomas did with some minor and in consequential changes.

(1) A group of individuals so constitutionally inferior that they will show symptoms under minor circumstances, they are basically below the normal standards of physical and nervous health.

(2) A group of persons essentially within normal limits of health but in whom symptoms appear after some physical trauma as gross overexertion or chronic fatigue and overwork, and who have not had sufficient rest and relaxation. Such cases are frequent in daily practice. The physician may observe minor symptoms in himself during a period of undue strain with insufficient rest. This will include not only the rapid pulse, increased tendency to perspiration, and other minor symptoms, but also the lack of initiative and concentrating ability. These symptoms will appear more readily in those who are less well endowed constitutionally. Sufficient

physical and psychic trauma will induce symptoms in the normal person.

(3) A group of patients who were well until the advent of some infection, or even a minor operation, followed by too short a period of convalescence.

(4) A group in which there is actually present some mild, silent, undiagnosed infection, such as an unrecognized tuberculosis, infected nasal sinuses, amebiasis, or any one of a group of undiagnosed infections. A mild hypoglycemia may predispose.

(5) A group in which the trauma is largely psychic, and in which there are doubts and fears which would be of small moment in those better endowed physically.

Care of the effort syndrome is the responsibility of the physician to whom the patient goes for help and advice. It should not be referred to the cardiologist or the psychiatrist. Nothing should be said or done to intimate to the patient that he or she is a cardiac or psychiatric problem, one of the great handicaps in treatment is that often the patient has already been told by some other physician that such is the case.

Each patient is an individual problem and cannot be managed by any set formula. Treatment does not require any special knowledge or armamentarium. What is required is common sense and a sympathetic understanding together with patience, firmness, and time. The physician should start

There will be some patients in the first category for whom he can do little, but whom he still can help. There will be some in the last category for whom he may need some help from the psychiatrist. But most of them he can help greatly and restore to a comfortable and useful life.

will tell the physician a great deal about the underlying conditions and what proportion of the symptoms are due to purely physical conditions and what proportion are due to an element of neurosis.

A careful, detailed physical examination will do much in the way of reassuring the

patient It will help to discover what previously undiagnosed mild or silent infection is present If present such infection should receive appropriate treatment but there should not be any witch hunt for so-called foci of infection unnecessary care of which will only add to the physical and mental trauma This is not to be construed to mean that actual sources of proved infection should not be cared for

Laboratory examination should be complete and may be fruitful A mild hypoglycemia may be discovered The fasting blood sugar should be determined it may be normal or too low values may be found after exertion or periods of nervous tension These may be improved by an appropriate high protein diet such as the Wilder diet

Treatment should be initiated by quiet friendly talks with the patient in which he is told exactly what the condition is and most important what it is not Such a talk should carry assurance of improvement but the patient must also be told that the improvement will be gradual and will depend greatly on his co operation He must understand that relief cannot depend on a few pills vitamins hormones or vaccines And he must not be told that his symptoms are imaginary for he knows better Some of the patients certainly as many as possible should be encouraged to continue their occupation with only the necessary modifications in their way of life and treatment should be simple so as not to attract the attention of the patient to symptoms of which he is already too aware

Many patients will require more rest and more hours of sleep than they are getting Sedatives should be avoided as far as is possible but a small dose of phenobarbital $\frac{1}{2}$

best omitted A mild carefully observed test exercise will reassure the patient and let him know that his heart is really not so bad An electrocardiogram may also be of reassurance to him

A program of physical exercise relaxation and entertainment should be worked out Both exercise and recreation should be supervised and should be increased by only small increments Overwork and overplay will only set the patient back

Many of these patients will best be cared

out in a rest camp provided with special facilities for rest physical therapy occupational therapy and recreation It is unfortunate that there are not more co operating agencies offering such supervised care where the patient will not have to associate with nervous invalids It is also unfortunate that city hospitals do not more frequently have associated country convalescent homes which are part of the parent hospital to which patients such as these could be sent to continue under the care of the physician in the parent hospital

Under a regimen of graduated exercise

Bertrand Smith and others

NEWELL C GILBERT

REFERENCES

- Gilbert N C and Fenn C K Effect of Digitalis on Coronary Flow *Arch Int Med* 50 668 1930
 Grant R T After histories of Men Suffering from Effort Syndrome *Heart* 12 121 1925
 Hope J A Treatise on the Diseases of the Heart and Great Vessels Philadelphia Haswell and Johnson 1840
 Kauffmann F Kreislauf und Nervensystem *Deutsche med Wchnschr* 59 989 1034 1121 1933
 Lewis Sir T *The Soldier's Heart and the Effort Syndrome* New York P B Hoeber 1919 Ed 2 London Shaw & Sons 1940
 Smith B *Physical Exercises in Use in the Cardio-*

adjust much better with rest before and after eating It may be better to have smaller meals with something additional between them Meals should be taken leisurely sitting quietly at a table not on a drugstore stool Medication directed to the heart or cardiac symptoms should not be given Supplemental vitamins may be advisable and often are necessary Tobacco and liquor are

CORONARY INSUFFICIENCY WITH ANGINA PECTORIS

Coronary insufficiency may be said to exist at any given time when the requirement of the myocardium for oxygenated blood exceeds the flow of blood to the myocardium of the heart. This situation may result from a single or a combination of a number of factors. Atherosclerosis of the coronary arteries is by far the most important lesion responsible for the production of coronary arterial insufficiency and our discussion in this chapter will be limited to the treatment of this condition. This pathologic process however may be present without the production of symptoms unless excessive demands are made on the heart by the superimposition of such conditions as excessive exertion, severe anemia, sudden hypertension, tachycardia or hyperthyroid

tated by reflex constriction of the coronary arterial tree (Blumgart). The recent injection studies of the coronary arteries in cases of coronary disease have served greatly to aid our understanding of the changing pathologic process in the coronary vascular bed in these cases (Blumgart, Schlesinger and Davis). The ability to develop collateral channels as a consequence of progressive coronary obstruction seems inherent in nature's scheme of preserving adequate myocardial nutrition.

The characteristic pain syndrome associated with transient brief insufficiency of the coronary arteries is called *angina pectoris*. When typical angina pectoris occurs without predisposing exertion the descriptive term *angina decubitus* is applicable. Prolonged attacks of anginal pain associated with greater systemic reaction but without evidence of myocardial infarction are properly designated as "acute coronary insufficiency" or "coronary failure" (Master). These episodes and also the occurrence of the anginal syndrome must be viewed with alarm as possibly indicating progressive

coronary disease or impending myocardial infarction (Boyer, Waltzkin).

Prevention Atherosclerosis of the coronary arteries may be said to be a universal disease since it is an accompaniment of aging. Coronary sclerosis is unfavorably influenced by simultaneously occurring obesity, diabetes and probably hyperlipemia. In recent years it has been suggested that a diet low in cholesterol content and the use of decholesterinization agents such as potassium iodide, lipocaine and choline might inhibit atherosclerosis (Hermann). These measures however have not as yet proved to be of significant benefit. Since a gap exists in our ability to prevent coronary atherosclerosis we can best meet the problem for those patients who are of middle age by reducing the work of the myocardium. The avoidance of obesity is particularly to be emphasized. The middle-aged man or woman should no longer partake of vigorous physical exertion to the extent that dyspnea and vigorous palpitation are produced. Similarly emotional moderation would seem of benefit. The patient in middle life who comes to his physician for advice should be impressed with the need for gradually reducing his responsibilities which lead to nervous tension. He should be advised to develop interests and hobbies which require less physical effort to replace the vigorous games and sports of his adolescence and young adult life.

General Measures of Treatment The physician's approach to the patient with coronary disease is of extreme importance. His consultation requires unusual tact in order to support the patient's morale and yet to stress firmly the importance of a careful regimen. The patient will benefit by a frank discussion apprising him that narrowing of the lumen of coronary arteries occurs in all persons as an accompaniment of age. He usually eagerly grasps with new hope a statement concerning the development of collateral circulation to assist the narrowed coronary arteries in nourishing the myocardium. A discussion in which instances of patients who have survived for many years of useful life are cited can be used to reassure the anxious patient to whom coronary disease often forebodes sudden death.

When symptoms of coronary insufficiency

are associated with specific etiologic factors other than coronary atherosclerosis such as anemia hyperthyroidism and syphilis these influences should be eliminated with suitable therapy

The patient with coronary insufficiency will be well aware of the predisposing situations which caused his distress. With these historical data it is the duty of the physician to attempt to lay out a specific program rather than merely to tell the patient to "take it easy." The patient with angina pectoris is too often dismissed with these words. As a result he may be completely confused concerning what he can or cannot do. This confusion helps cardiac neuroses to develop in persons who fear that every physical effort may provoke disaster. To the intelligent person it is often sufficient to offer the advice that he live in such a way that he stays within the tolerance of dyspnea and anginal distress. Most persons who have coronary insufficiency however will profit by more precise information. Specifically telling the patient that such things as shoveling snow, pushing a lawn mower or carrying a basket of clothes upstairs are hazardous will usually induce him to ask pertinent questions peculiar to his occupation which can then be discussed. This approach leads to a feeling of confidence in his physician which is of immeasurable value. The influence of cold air should be mentioned specifically as a precipitating factor of angina pectoris along with the comment that a scarf over the mouth and nose will largely avert attacks produced in this way. Increased cardiac work and angina pectoris may be induced in persons with coronary insufficiency by emotional upsets such as outbursts of temper and by witnessing exciting athletic contests. Moderation in emotional output together with avoidance of situations which induce excitement is the obvious advice needed. The avoidance of physical exertion after eating should be emphasized.

The physician who would treat coronary disease must not neglect the patient's other complaints and defects since they may have a profound influence on the course of the heart disease. There can be little doubt that symptomatic disease of the gallbladder, diaphragmatic hiatal hernia and peptic ulcers of the stomach and duodenum will

aggravate the symptoms of existing coronary insufficiency. Appropriate medical measures usually will counteract the influence of these conditions. Hypertrophy of the prostate with symptoms of obstruction which disturb the patient's needed rest may intensify the patient's cardiac disability and justify resection of the prostate. Chronic constipation and other manifestations of the irritable bowel syndrome are best treated with antispasmodics and gentle laxatives. This will prevent abdominal distention with associated anginal seizures.

Frequently the patient who has coronary disease is obese and this obesity offers both the physician and the patient a tangible problem to attack. The obese patient should be reduced by dietary restrictions to the average normal weight for his age and height. Gradual reduction in weight on a diet which provides 1000 to 1500 calories daily is better under these circumstances than is a rigid reduction regimen.

Patients with coronary disease fall prey to surgical diseases in about the same proportion as members of the general population. Unfortunately the presence of symptomatic coronary atherosclerosis increases the possibility of myocardial infarction at the time of operation or in the postoperative period. It is a good policy to advise the patient with angina pectoris against elective surgery of any type unless the lesion is potentially more serious than the cardiac disease or unless continuation of the surgical condition has a definite adverse effect on the heart. The presence of coronary disease of course should not contraindicate surgery which is necessary for the continuation of life. While the risk of operation will be increased that risk is justified for the removal of malignant tumors and for correction of such situations

which result in frequent and severe colicky pain and febrile reactions usually warrant surgical intervention because such attacks if repeated will be as detrimental as the trauma of surgery.

When surgery procedures are undertaken careful choice of anesthesia is indicated. The anesthetic agent used should r oxygen saturation in the resp

duration of the operation and the period of general anesthesia should be the least possible time. The blood pressure should be watched carefully in the operative and post operative period to prevent its falling to low levels since low blood pressure may be accompanied by myocardial ischemia. Administration of oxygen by mask or tent is usually advisable during the immediate postoperative period. Unless specific contraindications are present anticoagulant therapy with dicumarol during the postoperative period can be recommended for these patients on the justifiable assumption that the incidence of postoperative coronary thrombosis and thrombo embolic complications will be lessened.

Specific Measures of Treatment REST In the past years prescription of rest for patients with coronary disease without question has been much abused and has lacked intelligent application. The necessity of lessening the demands on the heart by adequate rest is of course obvious but the manner in which this is prescribed must be entirely dependent on the individual needs of the patient. In general the physician may justifiably recommend for the usual patient who has exertional anginal syndrome 9 hours of rest in bed each night and in addition a period of 1½ hours of complete relaxation during the afternoon. He should be advised to obtain a period of 30 to 60 minutes of complete relaxation on a couch or in a lounge chair following each meal since at those times the heart is called on for increased work in relation to the digestion of food. If anginal attacks of increased severity duration and frequency occur on less exertion a period of rest in bed for several days should be advised. Such progression of symptoms frequently is indicative of a progressive occlusive process with myocardial ischemia. Adequate rest and the use of suitable sedative
the
zone
larization to develop

TOBACCO It has been demonstrated quite conclusively that tobacco produces vasoconstriction in the arteries of the extremities (Roth, McDonald and Sheard). A similar action on the coronary arteries has been reasonably well substantiated by the demon-

stration of electrocardiographic changes of ischemia produced in susceptible patients through smoking (Bryant and Wood). Some patients with coronary insufficiency have observed that attacks of the anginal syndrome have been induced by smoking. It also has been demonstrated that smoking tobacco increases the carbon monoxide content of the blood and thus impairs the oxygen carrying capacity of the blood (Falk). On the basis of this direct and circumstantial evidence smoking should be discouraged for the patient with angina pectoris. The patient will accept the ban more gracefully and will cooperate better if he is apprised of the reasons listed for discontinuance of the use of tobacco. It is perhaps unwise for the physician to be too rigid in his demands of the patient with regard to the use of tobacco. There are patients for whom withdrawal of tobacco induces marked irritability and emotional tension and decreases cooperation for more important restrictions. For such individuals it is no doubt better judgment to encourage moderation in use of tobacco rather than complete withdrawal.

ALCOHOL When the physician has forbidden his patient with coronary disease the continuation of many of his previous pleas-

discovered by the patient as a means of obtaining relief from his chest pain even before he consults his physician. Clinically there is little doubt that 1 or 2 oz (30 or 60 cc) of whisky frequently will relieve the pain of coronary insufficiency probably because of its vasodilating as well as its anesthetic effect. If the patient is accustomed to the moderate use of alcohol and he finds that it is of aid in securing needed relaxation he may be advised to continue to use 1 to 2 oz two or three times daily. He must be warned that alcohol in excess may be of serious consequence by virtue of its action in depriving him of his ability to maintain proper restraint. In some individuals use of alcohol may be a factor in initiating abnormal cardiac rhythms and is to be avoided. Occasionally alcohol in the suggested doses will be of considerable value in preventing frequent attacks of angina decubitus.

Diet Instruction on diet for the patient

with angina pectoris should be designed primarily to prevent obesity and to cause him to avoid large meals which make excessive demands on the heart. The patient should take three or four small meals a day. Highly seasoned, fatty, and gas-forming foods should be taken in small quantities or not at all. Meals should be eaten slowly. Restriction of salt is not indicated in the diets of patients with coronary disease unless there is associated congestive heart failure which would profit by such restriction. A tendency toward constipation with associated abdominal distention and straining at the stool requires good bowel habits, the intake of sufficient fluid, and sometimes the use of mild laxatives such as mineral oil or milk of magnesia in doses of 1 to 2 tablespoons (4 to 8 cc). Considerable evidence indicates that individuals with known hyperlipemia may develop coronary atherosclerosis at an unduly early age and that the incidence of hyperlipemia is greater in patients with disease of the coronary arteries (Steiner and Domanski). Although a diet low in animal fat may not always lower the level of blood lipoids in these cases, foods rich in animal fat should be restricted.

DRUGS Specific medicaments for use in the treatment of coronary heart disease are as follows:

Barbiturates Nervous tension, which causes an elevation of the blood pressure, tachycardia, and probably also vasomotor cor-

of
pro-
on

seems to be best tolerated although continued use of barbiturate drugs should be avoided in the senile group of patients because they frequently produce mental confusion and irritability. The phenobarbital may be combined with a xanthine preparation if desired.

Nitrites Of the various nitrite drugs which act as vasodilating agents, nitroglycerin (glyceryl trinitrate) has proved the most valuable and most effective in the relief of anginal pain. The size of the tablets recommended should be the smallest which affords the patient relief and this may be $\frac{1}{100}$, $\frac{1}{50}$,

or $\frac{1}{100}$ grain (0.3 mg., 0.4 mg., or 0.6 mg.). It is necessary to instruct the patient in the use of nitroglycerin and not merely present him with the prescription. When anginal pain occurs, the tablet should be crushed with the teeth and then allowed to melt under the tongue. Fear of drug habituation prevents many patients from using nitroglycerin properly. Each patient may be advised that there is no evidence to indicate that repeated use as needed will lessen the effectiveness or produce dependence. When anginal pain occurs with unavoidable exertion, such as with the strain of defecation or with meals, the patient with regard to nitroglycerin should be the avoidance of repeated doses during a single

ischemia. Amyl nitrite perles (0.2 cc.) are faster in their action than nitroglycerin but are less convenient to handle and are more likely to cause disagreeable throbbing pain in the head and giddiness. Patients who have

doses or erythrityl tetranitrate in 30 to 60 mg. doses three to six times daily. In our experience they have not been of appreciable value.

Xanthine Drugs An extraordinary amount of controversy exists concerning the value of the xanthine preparations in the treatment of angina pectoris (Boyer, Harper). The intravenous injection of aminophylline (theophylline ethylenediamine) and theophylline with sodium salicylate has been demonstrated to enhance temporarily the tolerance of patients with angina pectoris to exercise and anoxia without pain (Bakst et al.). Clinically it seems to us that aminophylline in doses of $\frac{3}{4}$ or 7½ grains (0.25 or 0.5 gm.) given slowly intravenously once or twice daily is a valuable adjunct for patients who have severe coronary insufficiency as manifested by angina decubitus. Combining aminophylline with 250 cc. of 20 per cent glucose also can be recommended. Beneficial effects in similar patients occasionally may be obtained with the use of rectal

tories containing 7½ grams of aminophylline. The oral use of aminophylline which may be given in doses of 0.1 to 0.2 gm theobromine calcium salicylate in doses of 0.5 to 1.0 gm or other similar xanthine preparations is probably of little or no value and may produce gastric irritation and insomnia in some cases. The use of such preparations therefore must remain optional and if a trial fails to produce improvement continued use seems unwise and uneconomical.

Papaverine Papaverine hydrochloride occupies somewhat the same status as the xanthine drugs in the therapeutic armamentarium of patients who have angina pectoris.

In animals it has been demonstrated to increase coronary blood flow (Essex et al). There is quite general agreement that the intravenous administration of papaverine hydrochloride in doses of ½ to 1 grain (32 to 65 mg) is of value in relieving the pain of acute coronary insufficiency. The value of papaverine hydrochloride when administered orally is questionable. It may be recommended in doses of 1 to 3 grains (100 to 200 mg) three or four times daily to patients with angina decubitus or patients with coronary insufficiency with impending infarction. There is some evidence that it produces a quinidine like action in preventing auricular and ventricular extrasystoles and lessens the hazard of ventricular fibrillation especially after myocardial infarction. Unpleasant side effects such as drowsiness, vomiting and disturbances in cardiac conduction may occur.

Other Medications Several additional drugs have been favored in recent years because they were considered beneficial for coronary disease. Among these might be mentioned testosterone propionate (Luft and Malmstrom Lesser) and vitamin E (tocopherol) (Shute et al Vogelsang). In both instances early enthusiasm concerning the ability of these drugs to improve coronary circulation has not been verified by more critical evaluation (Levine and Likoff Levine and Sellers). Consequently until further investigation has been undertaken they cannot be recommended. Chemical thyroidectomy through the use of derivatives of thiourea has offered another medical approach founded on the beneficial effects originally reported in some patients with

angina following total thyroidectomy. The benefits which have been claimed have been attributed to the lowering of the level of metabolism and thus to the reduction of the demands on the heart muscle and the decrease in the sensitivity of the myocardium to epinephrine (Ben Asher Reveno Schoenewald). Both thiouracil (0.4 to 0.6 gm) daily and propylthiouracil (100 to 150 mg) daily have been found to reduce the basal metabolic rate and to decrease the frequency of anginal seizures in a number of patients. There are few cardiologists however who are enthusiastic about this mode of treat-

- (1) lessen the demands on the heart muscle
- (2) improve the vascularization of the myocardium and
- (3) relieve the pain of angina pectoris

Total thyroidectomy by surgical means has been done in an attempt to accomplish the first of these aims but this method of treatment has been abandoned even by its original proponents.

Improvement of cardiac vascularization has been attempted through grafting vascularized tissue, such as muscle fat or omentum onto the myocardium by producing an adhesive pericarditis with talc and by ligation of the great coronary vein (O'Shaughnessy Beck Thompson and Raisbeck Fauteux). The most recent of these attempts to improve circulation in the coronary arteries has been the anastomosis of a systemic artery to the proximally ligated coronary sinus (Beck et al). All of these procedures entail major thoracic surgery. Evaluation of the beneficial results of such procedures when weighed against the risks involved cannot be made at this time yet the recent dramatic advances in the field of cardiac surgery would indicate that further research in this direction may prove fruitful.

The surgical attack on the pain of coronary insufficiency is made possible by virtue of the fact that the afferent fibers from the heart enter the spinal cord through the dorsal roots of the upper four thoracic segments after traversing the corresponding sympathetic ganglia. Three methods are thus made avail-

able (White and Bland) The most used is the injection of the sympathetic ganglia with procaine followed by alcohol In most instances these injections must be bilateral This approach has the advantage of being least traumatic so that it may be attempted in patients for whom the risk of surgery is prohibited This method for the control of cardiac pain should be considered when control of pain proves impossible by medical means alone and frequent anginal attacks recur at rest and lead to physical exhaustion and extreme apprehension The majority of the afferent fibers from the heart pass through the stellate ganglia and stellate block alone has given relief to some patients Paravertebral injection of the first four or five thoracic sympathetic ganglia although a more technically difficult procedure than injection of the stellate ganglia alone has given more consistent relief of cardiac pain Alcohol block has the disadvantage of occasionally resulting in a painful neuritis involving the intercostal nerves More serious complications include pneumothorax and subarachnoid injection of the alcohol with transverse myelitis Thus these procedures cannot be recommended without proper evaluation of the patient's disability and recognition of the risks involved

More certain relief of pain may be accomplished by unilateral or bilateral thoracic sympathetic ganglionectomy or by section of the upper four or five thoracic dorsal roots Excellent relief of pain has been reported through both of these procedures Careful selection of candidates for these procedures is required and the risk involved must be evaluated properly Patients who have congestive failure or recent myocardial infarction should not be considered as likely candidates There seems to be adequate evidence that the fear of removal of a useful warning signal by these surgical procedures is without justification Patients who have had the pain pathways interrupted experience dyspnea pain in the jaw or other manifestations when they are exceeding the limits of their coronary circulation

Summary The fact that treatment for the patient with effort angina must be an individualized regimen should be emphasized again The primary goal at present must be

to utilize to the best advantage the coronary supply that is available and to institute those measures which in our present knowledge seem to encourage the development of additional coronary flow through collateral channels For the most part medication plays an insignificant role in the management of these patients Except for mild sedation for the nervous or emotionally tense individual and the use of nitroglycerin when necessary for relief of anginal distress medication is of little proved value Prescribing a number of pharmaceutical preparations is more likely to reflect the physician's enthusiasm for the drugs than his understanding of their expected effect The physician who is able to instruct his patient in the need for mental and physical self control with the avoidance of fatigue and who can instill respect for the need of moderation in habits of work and play without arousing unwarranted fear and self concern will prove more successful in delaying the progression of coronary insufficiency than the physician who has undue enthusiasm for the beneficial effects of the large number of pharmaceutical preparations available for the treatment of the anginal patient

MILTON W ANDERSON
ROBERT L PARKER

REFERENCES

- Balst H et al The Effect of Intravenous Aminophylline on the Capacity for Effort Without Pain in Patients with Angina of Effort *Am Heart J* 36 527 1948
- Beck C S Principles Underlying the Operative Approach to the Treatment of Myocardial Ischemia *Ann Surg* 118 788 1913
- Beck C S et al Revascularization of Heart by Graft of Systemic Artery into Coronary Sinus *JAMA* 137 436 1948
- Ben Asher S Further Observations on Treatment of Anginal Syndrome with Thiouracil *Am Heart J* 33 490 1947
- Blumgart H L The Question of "Spasm" of the Coronary Arteries *Am J Med*, 2 129 1947
- Blumgart H L Schlesinger M J and Davis D Studies on Relation of Clinical Thrombosis and Myocardial Infarction to Pathologic Findings with Particular Reference to Significance of Coronary Thrombosis
- Boyer N H Premortuary Symptoms of Myocardial Infarction *New England J Med* 227 623 1942

be discouraged. The presence of a pre-existing anginal syndrome is more likely to lend emphasis to the necessity of these alterations.

including rest in bed, the use of coronary vasodilating drugs, sedation, and, when feasible, anticoagulant therapy with dicumarol.

Aims in the Therapy of Acute Myocardial Infarction. The first aim of therapy in cases of myocardial infarction is the relief of pain and the avoidance of shock. The second aim of therapy is directed toward the improvement of nutrition of the ischemic myocardium. Because of the occlusive process cardiac nutrition is partially or completely interrupted in a segment of the myocardium. While it has been assumed that further embarrassment to the myocardium may occur from reflex vasoconstriction of the coronary arterial tree, recent experimental work on animals has indicated the absence of such a mechanism (Opdyke and Selkurt). To assume an absence of reflex vasoconstriction in the human being with acute occlusion and that it does not play a significant role in the acute pain of myocardial infarction seems hardly in accord with clinical experience. The third aim in the therapeutic attack is to reduce the work of the heart and the various complicating phenomena.

General Consideration of Treatment. The suspicion that acute infarction of the myocardium is present is the first indication for instituting proper therapy. It is wiser to err by instituting proper treatment for acute myocardial infarction while the diagnosis is temporarily in doubt than to delay until clinical findings establish the diagnosis beyond question. An attack of severe anginal pain persisting for 30 minutes or longer, particularly if spontaneous in origin and associated with weakness and perspiration, indicates the need for inaugurating therapy until electrocardiographic or other laboratory evidence proves or disproves the presence of myocardial infarction.

It is not advisable to establish a definite routine for the management of all patients

with acute myocardial infarction since treatment must at all times be individualized. We might, however, consider certain measures which are indicated during the acute phase in most instances of acute coronary insufficiency with myocardial infarction.

Relief of pain is the first requirement. Although one of the newer synthetic preparations may be tried, clinical experience would indicate that morphine is the most satisfactory drug for this purpose. At least $\frac{1}{2}$ to $\frac{1}{4}$ grain (15 to 30 mg) of morphine sulfate, administered hypodermically, is usually required and is best combined with $\frac{1}{10}$ to $\frac{1}{8}$ grain (0.4 to 0.8 mg) of atropine sulfate. The administration of morphine should be followed by the intravenous administration of either $\frac{7}{8}$ grains (0.5 gm) of aminophylline or 1 grain (0.065 gm) of papaverine hydrochloride. Both of these

should be controlled when the patient can be hospitalized. Transportation to the hospital is usually more feasible after the pain has been brought under control with sufficient opiate and after restlessness and apprehension have been relieved. Transportation by ambulance should be arranged for when this is possible. The patient should be kept warm and in the position which he finds most comfortable. Except in those cases in which the picture of peripheral shock is dominant the patient is usually most comfortable with the head of the bed moderately elevated. Additional opiates may be required after the patient has been admitted to the hospital, but a word of caution is in order against the insistence of deep narcosis beyond that required for the relief of pain and restlessness.

There is some difference of opinion regarding the advisability of oxygen inhalation for all patients even when shock, cyanosis, or dyspnea is not present. If the patient can be assured under such circumstances that oxygen is being prescribed as advisable medication and does not reflect a moribund state, he will usually co-operate and find comfort in the cool atmosphere of an oxygen tent. If he prefers, an oxygen mask may be used. Although clinical evidence of anoxemia may not be present, there is probably sufficient theoretical advantage in maintaining a

high oxygen saturation of the arterial blood to advise the use of oxygen during the first few days in all cases (Barach and Levy)

Brief questioning of the patient or his relatives will usually determine whether or not there has been an antecedent history of bleeding peptic ulcer renal disease or hepatic disease which would contraindicate anticoagulant therapy. Laboratory procedures which should be performed immediately include urinalysis and determination of the concentration of blood urea. In the absence of contraindication which will be considered in detail later and if laboratory facilities are available for the accurate determination of the prothrombin time anticoagulant therapy should be started at once.

General Therapeutic Measures. REST

Physical and mental rest must still be considered of prime importance in the treatment of myocardial infarction to allow the myocardium to maintain circulation at as close to basal conditions as possible. In our opinion the duration of rest in bed and the degree of limitation while the patient is in bed must be individualized depending on the severity of the attack and the presence or absence of complications. During the first 2 weeks the patient should not be disturbed by frequent or vigorous physical examination. It is possible to examine the heart most of the lungs and the abdomen gently without disturbing the patient. This cursory type of examination usually is adequate for following the course of the illness. Examinations such as pelvic and rectal examinations which may cause pain and psychic disturbances should be deferred. Mental rest during the first week can be abetted by preventing visits to the patient except by immediate members of the family whose visits should be brief. The extreme degree of limitation of activities which has been recommended in the past for the patient with acute myocardial infarction is probably not too well founded. Certainly the patient with precarious cardiac compensation and severe systemic symptoms should not be permitted to exert unnecessary muscular effort. Such a patient should be fed and turned in bed by the nursing staff and should be given sufficient sedative to ensure rest during the first week or two when his condition is most critical. It is unwarranted, however, to prevent

the patient whose occlusive process is not accompanied by shock prolonged pain or severe systemic reaction from feeding or turning himself. The anxiety created in such a patient by complete immobilization may increase cardiac work to a greater extent than permitting him to do a few things for himself. It should however be firmly stressed that he is to remain in bed during this acute phase. Co-operation in this regard is best obtained by a frank explanation concerning the softened myocardium which requires time to heal by fibrosis.

The duration of rest in bed will vary with the severity of the illness and the progress of recovery. Probably the minimal period of rest in bed should be 3 weeks even in the case in which clinical reaction is mild. The course is uncomplicated and serial electrocardiograms reveal rapid evolution toward normal. The majority of patients with severe myocardial infarction which is uncomplicated by extension of the infarction arrhythmia or congestive failure should rest in bed for 4 to 6 weeks. By this time the sedimentation rate of the erythrocytes usually has reached normal and the electrocardiograms show stabilization with a relic pattern. When the course is complicated by recurrent infarction pulmonary embolism or by the development of cardiac decompensation it may be necessary to prolong the period of rest in bed for several additional weeks. Elderly persons should be allowed to sit up and the period of strict immobilization should be made as short as possible to ward off the occurrence of hypostatic pneumonia and other similar geriatric complications. From the foregoing consideration it is apparent that no set rule can be established concerning the recommended duration of rest in bed. Recently in contrast with the conservative treatment in general use there has been a trend toward shortening the period of rest in bed. In our opinion a compromise between these two views has proved to be most satisfactory.

When the period of restriction in bed for a specific patient is believed to be completed his return to more activity must be gradual. At first he is permitted to sit in a comfortable chair for 15 to 30 minutes two or three times a day. The patient should be observed carefully during this change in his routine. The

DISEASES OF THE CARDIOVASCULAR SY

appearance of excessive tachycardia or recurrence of definite anginal distress or dyspnea would indicate that further rest in bed is probably advisable. If he tolerates sitting up without incident its duration can be extended daily so that, in the course of a week, he may be able to be up several hours daily and may take a few steps about his room. When he has regained sufficient strength to be able to walk about the room and change from a lounge chair to his bed unaided and with ease convalescence usually can be safely continued at home.

DIET. It is generally agreed that ingestion of food increases cardiac work. Experimental observation would indicate that distention of the stomach aggravates coronary insufficiency, probably by reflex coronary vasoconstriction. This physiologic observation and also the relative frequency of nausea vomiting and abdominal distention immediately following an acute myocardial infarction warrant consideration of dietary management. During the immediate acute episode when shock, pain and nausea and vomiting may be present, only liquids may be tolerated. As improvement occurs usually within the first week, a soft diet is substituted with the precaution that feedings should be small. Subsequently the caloric value of the diet will vary with the state of nutrition of the patient. During the first week the intake in any case should not be more than 1200 to 1500 calories per day. In cases in which the patients are obese, a daily diet of 1000 calories is advisable during hospitalization and during the subsequent convalescence until the weight of the patient has been reduced to normal. Vitamin supplements such as one of the multiple vitamin preparations should be taken daily while the caloric intake is restricted. When obesity is not a problem and when the convalescence is proceeding without incident a general diet should be allowed with no restriction of particular foods except those which may be classified as gas-producing foods and those known to be poorly tolerated by the patient. Portions

great deal of value, on the one discomfort on the patient use a bed using the bed requires excessive use namely, to. Some patients are allowed with the use of a bedstents who are continuous use those who are to bed pan continue. Abdominal distention after acute infarction simple abdominal tube if necessary and similar drug-cated. During the acute myocardial be made to induce bowel movement tion is causing distention not moved spontaneously fifth day of the illness encouraged with milk of magnesia 1 to 2 oz (30 to 60 cc) to produce a bowel movement warrants the use of a saline enema per 2 oz (60 cc) of oil which has been Bulk-producing purgatives are to

FLUID INTAKE. In the case of a myocardial infarction no serious problem of nausea and vomiting as a sequence of the sensitivity of the patient to pain may develop and administration of 0.9 per cent solution or in combination

of its excess of chloride ion will be of value in replacing chloride lost by vomiting and the dextrose serves as a nutrient for the heart muscle

Drug Therapy OPIATES As previously indicated morphine sulfate has proved to be the most satisfactory of the various opiates for relief of the severe pain of acute myocardial infarction. Persistence of intense pain is not only unbearable to the patient but also may be a factor in producing reflex coronary vasoconstriction as well as shock (Kistner and Mazer). A hypodermic injection $\frac{1}{4}$ grain (15 mg) or more of morphine sulfate usually will be required to control the pain. This may be repeated in 30 minutes if necessary and thereafter at intervals of 3 or 4 hours if pain is not relieved. In some cases the intravenous administration of morphine may be indicated. In place of morphine $\frac{1}{4}$ to $\frac{1}{2}$ grain (15 to 30 mg) of pantopon (a preparation containing the total opium alkaloids in the form of soluble hydrochlorides) may be administered hypodermically or $\frac{1}{32}$ to $\frac{1}{16}$ grain (2 to 4 mg) of dilaudid hydrochloride may be given by the same method.

The use of opiates in the treatment of myocardial infarction has been criticized on the basis that these drugs may increase vagus spasm, depress respiration and cause abdominal distention. Undoubtedly the greatest disadvantage of morphine sulfate and related drugs is the production of vomiting in sensitive persons. Such an unfavorable reaction may be avoided by questioning the patient or members of the family about previous undesirable reactions to opiates. If the patient has had such a reaction one of the newer synthetic analgesics may be substituted.

The above

ministered intravenously or intramuscularly. The oral administration of papaverine hydrochloride has been advocated to prevent cardiac irritability but whether the drug produces any significant benefit when given orally is open to question. We believe papaverine hydrochloride has a definite place in the immediate treatment of acute coronary insufficiency. Frequently when it is administered slowly by the intravenous route it

produces dramatic relief from the crushing pain and may make the use of other opiates unnecessary. It certainly should be given in preference to morphine when there is a history of previous unpleasant reactions from morphine sulfate. The administration of papaverine hydrochloride may be repeated in 30 minutes if there is recurrence of pain. The

tiously or not at all in the presence of peripheral vascular collapse. When papaverine hydrochloride is given too rapidly vomiting and hypotension may occur consequently slow administration is necessary.

XANTHINE DRUGS In our opinion the oral administration of xanthine preparations such as aminophylline, theobromine sodium acetate or theobromine calcium salicylate is of little or no value for the patient with acute myocardial infarction. Aminophylline (theophylline ethylenediamine) administered intravenously however is effective in increasing coronary blood flow and is a valuable preparation. In the event of prolonged pain and also in the presence of nocturnal dyspnea or pulmonary edema this drug deserves adequate trial. It should not be injected rapidly. It may be given in doses of 3% to 7% grains (0.25 to 0.5 gm) either alone or in combination with 100 to 200 cc of 20 per cent solution of dextrose by intravenous drip. Either aminophylline or papaverine hydrochloride

in the event of recurrent anginal pain. As previously stated aminophylline and papaverine should not be given simultaneously.

BARBITURATES Sedation with barbiturates is indicated during convalescence from myocardial infarction in order to insure sleep and to suppress anxiety. Phenobarbital may be administered orally in doses of $\frac{1}{4}$ to $\frac{1}{2}$ grain (0.016 to 0.032 gm) two or three times a day as needed to assist the patients to relax while they are awake. It is unwise however to administer sedatives in doses larger than necessary to produce relaxation. The tendency of some physicians to keep patients with acute infarction "snowed under" for days is to be deplored. Caution must also be used in prescribing barbiturates to aged patients

owing to the tendency of these drugs to produce confusional states

ATROPINE SULFATE It is not entirely agreed how effective neurogenic mechanisms are on the coronary vessels and coronary blood flow in man. The results of various experimental studies in animals are not in agreement. Some cardiologists advocate the use of atropine sulfate by hypodermic injection in repeated doses during the first few days of acute myocardial infarction. It is assumed that this drug, by inhibiting vagal action, suppresses reflex vasoconstrictive impulses to the coronary arteries and also prevents dis-

tachycardia, we are not enthusiastic about its use except in accompaniment with hypodermic injection of opiates for the relief of pain. We prefer to administer quinine sulfate when there is indication of increased myocardial irritability.

ALCOHOL Whisky or brandy may be prescribed in small amounts especially for patients who are accustomed to the use of alcoholic beverages. Patients who note residual thoracic discomfort after the severe anginal pain has subsided may be benefited by alcohol. It has the beneficial effects of alleviating apprehension and promoting relaxation.

NITRITES During the acute phase of myocardial infarction glyceryl trinitrate, amyl nitrite, and the other nitrites are of little value in relieving pain. Their repeated administration in the presence of suspected infarction should be avoided because of their tendency to produce hypotension and to increase shock.

ANTICOAGULANT THERAPY Experience in the past few years regarding the use of anticoagulants has without exception served to emphasize the value of dicumarol in the treatment of patients with acute myocardial infarction. The high incidence of thromboembolic complications as an aftermath of acute myocardial infarction has been one of the main factors in contributing to a high mortality and high morbidity rate (Nav and Barnes). These complications result from secondary thrombotic occlusions in the coronary arterial tree with extension of infarction, mural thrombus with arterial emboli, throm-

bophlebitis with pulmonary embolism, and in situ thrombosis of other arteries already affected by atherosclerosis. Anticoagulant therapy, effectively controlled, will certainly reduce the hazard of complication of this type. Recent investigations have shown that dicumarol does not adversely affect myocardial repair after infarction and does not cause an increase in myocardial hemorrhage or necrosis (Blumgart et al.). Apprehension in this regard has previously caused some physicians to be reluctant to employ anticoagulant therapy. The same apprehension has been expressed concerning the role of subintimal hemorrhage in the production of acute arterial occlusion with secondary thrombosis. Pathologic studies have shown that small hemorrhagic areas occur not infrequently in the subintimal atheromatous plaques of coronary vessels affected by atherosclerosis. Actual closure of the arterial lumen by free bleeding into one of these areas resulting in displacement of the intima is not common. One might well anticipate finding this type of lesion particularly in cases of fatal acute infarction in which anti-

the enthusiasm for anticoagulant therapy.

There are two preparations available for producing an anticoagulant effect on the blood. The administration of both of these preparations requires supervision. Neither preparation possesses the qualities which one would desire in an ideal anticoagulant. Heparin is expensive and its effect is of brief duration. It, therefore, has to be administered continuously or at frequent intervals by the

more difficult to control and it may cause bleeding at the site of injection. It is seldom justifiable to administer heparin for more than a few days and, fortunately, this is not necessary when it is administered with dicumarol.

Dicumarol is inexpensive and also has another advantage, that is, it can be administered orally. It also has some disadvantages. Daily determinations of the prothrombin time are necessary to control the dosage of this drug. Another disadvantage is that

effect is delayed for 24 to 72 hours after its administration is started and the effect may persist for from 2 to 7 days after administration of the drug is discontinued. Furthermore there is a wide variation in the sensitivity of patients to dicumarol. To be effective the dosage of the drug should reduce the prothrombin activity to between 10 and 20 per cent of normal and should maintain it at this level. When the dosage is properly controlled the risk of bleeding is negligible but the possibility of this complication should always be kept in mind. Major bleeding can usually be controlled promptly by intravenous administration of 60 mg of synthetic vitamin K and by the transfusion of fresh citrated whole blood.

Are both heparin and dicumarol necessary in the usual case of acute myocardial infarction? This question has not been satisfactorily answered as yet by clinical experience. The only justification for employing heparin in addition to dicumarol is to obtain the immediate anticoagulant effect which heparin produces and to continue this effect until dicumarol produces an optimal decrease of the prothrombin activity. How necessary is it then to obtain an immediate anticoagulant effect during the 1 to 3 days before dicumarol becomes effective? It has been shown that thromboembolic complications seldom occur before the fifth day after the onset of acute myocardial infarction. Thus in most instances dicumarol alone should be sufficient. Because of the greater likelihood of an extension of the thrombotic process in the coronary arterial tree or other vascular complications in those cases of myocardial infarction in which the clinical picture is one of shock with marked hypotension and slowing of circulation and hemoconcentration it would seem justifiable to use heparin for its immediate effect in addition to dicumarol. In cases of acute coronary occlusion in which this profound systemic reaction does not occur and in cases in which patients enter the hospital several days after the onset of clinical evidence of acute infarction heparin is probably not necessary.

Contraindications to Administration of Dicumarol. The first contraindication to dicumarol therapy is lack of proper laboratory facilities for accurate determination of the prothrombin time. Emphasis must be placed

on the fact that it is not safe to initiate treatment

In cases in which renal and hepatic insufficiency are present the effect of dicumarol may be greatly accentuated and difficult to control; therefore dicumarol therapy should be omitted. (We have found it advisable to examine the urine and to determine the concentration of blood urea before starting the administration of dicumarol. A slight elevation of the value for the blood urea does not contraindicate the administration of dicumarol but it is wise under such circumstances to reduce the initial dose to 100 or 200 mg until the patient's sensitivity to the drug can be determined.) A history of peptic ulcer or known ulcerative lesion of the gastrointestinal tract should preclude its use and it should be avoided in purpura or blood dyscrasia. It should be used with caution in those cases in which the diet has been markedly restricted for several days and in cases in which prolonged nausea and vomiting have caused a definite nutritional deficiency. In such cases the patients frequently are hypersensitive to the drug.

Administration of Anticoagulants. In the majority of cases of acute myocardial infarction we have not felt it advisable to give both heparin and dicumarol except under the circumstances previously mentioned. If both heparin and dicumarol are to be used the following schedule may be suggested: 300 mg of dicumarol are given orally when the patient is admitted to the hospital or as soon as the clinical diagnosis of acute coronary occlusion has been made and contraindications to the administration of the drug have been excluded. At the same time 50 mg of heparin are given intravenously and repeated at intervals of 4 hours. The prothrombin time is determined every morning. If there is only a negligible increase in the prothrombin time on the morning after the administration of the initial dose 200 mg of dicumarol may then be given. If however the prothrombin time indicates a drop in the

* A new form of depot heparin is now available. 200 mg are administered intramuscularly once or twice in 24 hours depending on the coagulation time as determined by the Lee-White method.—*Editor*

level of prothrombin activity to approximately 50 or 30 per cent of normal, the administration of dicumarol is omitted on the second day in order to avoid an undue suppression of prothrombin activity in what would appear to be more than a usually sensitive patient. The administration of heparin is discontinued when the prothrombin time taken 3 hours after the last injection of heparin indicates that the prothrombin activity is 30 per cent of normal. Subsequent to the second day, 50 to 200 mg of dicumarol are given orally on those days on which the prothrombin time indicates that the prothrombin activity is greater than 20 per cent of normal and the administration of the drug is omitted on those days on which the prothrombin activity is less than 20 per cent of normal. In some cases a dose of 200 mg may have to be administered daily to maintain the prothrombin time at the desired level. In other cases this effect may be obtained by

age by daily determination of the prothrombin time.

It has been our policy to continue anti-coagulant therapy as long as the patient is confined to the hospital. Although theoretical considerations would strongly suggest continuation of this therapy throughout the convalescent period it has not been practical as yet to carry out a program of this type. Perhaps further investigation will result in the development of an anticoagulant which is as effective as dicumarol but which is more easily controlled. Although a decrease of the prothrombin activity to almost zero (prothrombin time of 70 to 100 seconds when 60 seconds represent prothrombin activity that is 10 per cent of normal) is rarely associated with bleeding manifestations such a decrease is a cause for concern. When it is encountered, 25 to 72 mg of menadione bisulfate

occlusion as well as in the treatment of acute myocardial infarction.

Complications of Myocardial Infarction
Shock. Profound shock in association with myocardial infarction usually denotes a poor

cardium and diminished cardiac output. In many cases, the symptoms of shock will be alleviated by the administration of oxygen plus the relief of pain by measures outlined previously. Whether or not treatment of shock by increasing circulating blood volume is indicated when the primary disturbance is myocardial in origin remains a debatable point. In our experience the slow administration of 300 to 500 cc of plasma or whole blood by the intravenous route occasionally has been of definite value in patients with profound shock.

CARDIAC ARRHYTHMIA *Extrasystoles.* The occurrence of frequent extrasystoles, particularly if they can be demonstrated to arise from the ventricular myocardium, may portend ventricular tachycardia or fibrillation. Administration of quinidine sulfate in doses of 3 grains (0.2 gm) three or four times daily is indicated under these circumstances and will in most instances abolish these signs of cardiac irritability. We have not found it advisable to use quinidine routinely unless evidence of cardiac irritability was present.

Ventricular Tachycardia. This is an ominous complication which may lead to sudden death from ventricular fibrillation. Therapy with quinidine sulfate should be adequate

every 2 hours until the tachycardia terminates or until quinidine intoxication occurs. If the attack terminates as a result of this therapy, 3 grains (0.2 gm) of quinidine sulfate should be administered four times daily during convalescence.

Auricular Fibrillation and Auricular Flutter. In the absence of congestive heart failure,

dosage, dicumarol and when advisable, both heparin and dicumarol has resulted in the most significant single advance in recent years in the treatment of impending coronary

the development of auricular fibrillation or auricular flutter likewise warrants an attempt to convert the arrhythmia to sinus rhythm with quinidine alone. Even though normal rhythm is re-established administration of quinidine

congestive heart failure with pulmonary congestion and retention of fluid may occur even while the patient is at complete rest. This unfortunate complication indicates severe damage to the myocardium and poses a difficult therapeutic problem. The intake of sodium should be restricted when there is evidence of retention of fluid. A diet with sodium content of 0.5 gm is satisfactory. The appearance of basal pulmonary rales should be a warning that acute pulmonary edema is likely to develop. Pulmonary congestion is benefited by the slow intravenous injection of 7½ grains (0.5 gm) of aminophylline (theophylline with ethylenediamine) in 200 cc of a 20 per cent solution of dextrose two or three times daily. Oxygen in high concentrations is of value in relieving dyspnea; it preferably should be used before pulmonary edema occurs. The intravenous or intramuscular injection of one of the mercurial diuretics in the usual doses may be of value when there is evidence of retention of fluid but should be avoided when there is marked hypotension with a low output of urine. When acute pulmonary edema occurs morphine should be given in addition to oxygen and aminophylline.

In spite of these measures it may be impossible to maintain cardiac compensation without the use of digitalis. Traditionally digitalis has been considered to be contraindicated in cases of acute myocardial infarction because of the fear that it might cause myocardial rupture, ectopic rhythm, and

ent study
duce car
ut that it
was likely to increase the incidence of thromboembolic phenomena (Askey and Neurath). The latter complication can now be largely avoided by the use of dicumarol. In our opinion it is most unwise to withhold digitalization when it becomes obvious that congestive failure cannot be controlled without it.

Digitalis should be administered orally unless rapidly progressive acute pulmonary edema necessitates intravenous administration. The preparation of choice should be the one with which the attending physician has the most experience. Digoxin or one of the purified glycosides is usually recommended. An initial oral dose of 0.6 mg of digoxin should be followed in 8 to 12 hours by a dose of 0.4 mg. Subsequently 0.1 to 0.2 mg should be administered daily unless there is evidence that this dose is insufficient or excessive.

DIABETES MELLITUS Glycosuria may occur as a transitory finding during acute myocardial infarction and as such does not denote that diabetes mellitus is present. Knowledge of this occasional finding is of importance because the administration of insulin for such glycosuria is unnecessary and may be hazardous. Myocardial infarction in a diabetic patient will require careful supervision of the diabetes. It is essential to avoid hypoglycemic reactions and it is wiser to permit moderate hyperglycemia and slight glycosuria to develop during the first few weeks of myocardial infarction than to entail the risk of hypoglycemic reactions.

SHOULDER HAND SYNDROME One of the most baffling complications which is frequently encountered in patients recovering from acute myocardial infarction is unilateral or bilateral painful fixation of the soft tissues of the shoulders which often is associated

al) It can best be classified as a neurocirculatory dystrophy. It is commonly called the shoulder hand syndrome. Treatment has been of two main types. First conservative management with heat, gentle massage and passive exercises should be tried. The failure of conservative measures to give relief and the continuation of severe pain warrant interruption of the sympathetic innervation by injection of procaine hydrochloride into the stellate ganglion or of the first three or four thoracic sympathetic ganglia. Repeated block by this means may be necessary and sympathectomy may be necessary in some cases.

After Care of the Patient The after-care of the patient who has recovered from the acute phase of myocardial infarction consists

primarily of an individualized guidance program to return the patient to a useful and productive life. Certainly, the rest program should be continued after the patient leaves the hospital. Generally, the patient should remain at home for from 4 to 8 weeks after he leaves the hospital. Patients seldom should be permitted to return to work, even on a part time basis, in less than 12 weeks, even though the work is of a sedentary type. Resumption of increasing hours of work and responsibilities should be gradual, and the necessity for assuming a lowered level of activity and a less competitive philosophy of life should be emphasized just as important as the necessity for reassurance and optimism that an enjoyable and productive life is possible. Whether or not an anginal syndrome develops after recovery from acute infarction adequate daily rest is important. The patient should be advised to obtain at least 9 hours of rest in bed each day and to continue a daily rest period of an hour or two each afternoon. The avoidance of both nervous and physical fatigue and continued moderation in eating, drinking, and smoking also should be emphasized.

The degree of physical disability following the recovery phase of acute myocardial infarction will, of course, vary greatly. One patient may be completely incapacitated with little evidence of myocardial reserve, whereas another patient may have little symptomatic or objective evidence of unpaired cardiac function. Obviously, guidance in each case will have to be individualized depending largely on the physician's judgment of the existing cardiac reserve.

ROBERT L. PARKER
MILTON W. ANDERSON

REFERENCES

- Askey, J. M., and Neurath, O. Is Digitalis Indicated in Myocardial Infarction? *JAMA*, 123 1016 1945
- Barach, A. L., and Levy, R. L. Oxygen in Treatment of Acute Coronary Occlusion. *JAMA*, 103 1690 1934
- Blumgart, H. L., et al. The Effect of Dicumarol on the Heart in Experimental Acute Coronary Occlusion. *Am Heart J*, 36 13, 1949
- de la Chapelle, C. E. Management of Acute Episode in Coronary Occlusion. *Bull New York Acad. Med*, 19 201, 1943
- Elek, S. R., and Katz, I. N. Some Clinical Uses of Papaverine in Heart Disease. *JAMA*, 120 434, 1942
- Essex, H. E., et al. Effect of Certain Drugs on Coronary Blood Flow of Trained Dog. *Am Heart J*, 19 554, 1940
- Gilbert, N. C., Fenn, G. K., and LeRoy, G. V. Effect of Distention of Abdominal Viscera on Coronary Blood Flow and on Angina Pectoris. *JAMA*, 115 1962, 1940
- Greisman, H., and Marcus, H. M. Acute Myocardial Infarction, Detailed Study of Dicumarol Therapy in 75 Consecutive Cases. *Am Heart J*, 36 600, 1948
- Harrison, T. W. Abuse of Rest as Therapeutic Measure for Patients with Cardiovascular Disease. *JAMA*, 125 1075, 1944
- Kistin, A. D., and Mazer, M. Current Practice in Cardiovascular Diseases, Treatment of Acute Myocardial Infarction. *M. Bull. Vet. Admin.*, 19 369, 1943
- LeRoy, G. V., Fenn, G. K., and Gilbert, N. C. Influence of Xanthine Drugs and Atropine on Mortality Rate after Experimental Occlusion of Coronary Artery. *Am Heart J*, 23 637, 1942
- Nay, H. M., and Barnes, A. R. Incidence of Embolic or Thrombotic Processes during Immediate Convalescence from Acute Myocardial Infarction. *Am Heart J*, 30 85, 1945
- Nichol, E. S. Treatment of Acute Coronary Thrombosis with Dicumarol, Further Observations. *Am Heart J*, 33 722 1947
- Nichol, E. S., and Page, S. W., Jr. Dicumarol Therapy in Acute Coronary Thrombosis. Results in 50 Attacks with Review of Data on Embolic Disease. *Am Heart J*, 33 10 1947
- Parker, R. L., and Barker, N. W. Use of Anticoagulants in Management of Acute Myocardial Infarction. Preliminary Report. *Proc Staff Meet., Mayo Clin*, 22 185 1947
- Peters, H. R., Guyther, J. R., and Brambel, C. E. Dicumarol in Acute Coronary Thrombosis. *JAMA*, 130 393, 1946
- Steinbrocker, O., Spitzer, N., and Friedman, H. H. The Shoulder Hand Syndrome in Reflex Dystrophy of the Upper Extremity. *Ann Int. Med.*, 29 22 1918
- Wright, I. S. Experiences with Dicumarol (3, 5'-methylenebis [4-hydroxycoumarin]) in Treatment of Coronary Thrombosis with Myocardial Infarction. Preliminary Report. *Am Heart J*, 32 20, 1946
- Wright, I. S., and Foley, W. T. Use of Anticoagulants in Treatment of Heart Disease with Special Reference to Coronary Thrombosis. Rheumatic Heart Disease with Thrombo-embolic Complications and Subacute Bacterial Endocarditis. *Am J Med*, 3 718, 1947

SUBACUTE BACTERIAL ENDOCARDITIS

Until the introduction of penicillin the treatment of subacute bacterial endocarditis was inadequate and discouraging. It was estimated that at most 1 per cent of the cases had a spontaneous remission. With the advent of the sulfonamides the rate of cure rose to between 4 and 6 per cent. The use of the sulfonamides with heparin and with hyperthermia was said to result in a somewhat higher rate of recovery. However, at best only 10 per cent of patients survived.

With the use of penicillin the outlook for these patients changed radically. As soon as adequate amounts of penicillin were available reports of cures began to appear in the literature in approximately 70 to 80 per cent of cases.

Etiologic Organisms In the treatment of subacute bacterial endocarditis it soon became evident that the type of organism and its susceptibility to antibiotics were of the greatest importance. In the earlier cases most successful results were usually obtained when the organisms were extremely sensitive to penicillin. However, it soon became apparent that resistant organisms could be adequately handled by using large amounts of penicillin.

Fortunately approximately 90 per cent of cases are caused by the alpha streptococcus (viridans). This organism is usually extremely sensitive to penicillin. Seven per cent of cases are caused either by the gamma streptococcus, the beta hemolytic streptococcus, the enterococci, or a nonhemolytic streptococcus (the streptococcus sbe). As a rule the organisms in this group are relatively insensitive. The remainder of cases have as their etiologic agent a gram negative bacillus such as the influenzal organism and a variety of other bacteria. These organisms are usually insensitive to penicillin but may be quite susceptible to streptomycin, to a sulfonamide, to aureomycin or chloromycetin.

Isolation and Determination of Characteristics of Organism In treating subacute bacterial endocarditis the first step is culture of the organism or organisms involved. Occasionally in a particular case more than one organism is the cause of the disease. The sensitivity to penicillin must

be determined for all organisms. Of the various methods in use the serial dilution test is probably as quick and as satisfactory as obtaining significant results with a minimum of errors. In each case a control is made with a standard strain of *Staphylococcus aureus* of known sensitivity (*Staphylococcus aureus* HMB 109). The usual bacteriostatic level of a penicillin sensitive organism is 0.01 to 0.1 oxford units per cubic centimeter. A range up to 10 oxford units per cubic centimeter is considered moderately sensitive. Anything above 10 must be considered relatively penicillin resistant. If the organism shows an in vitro sensitivity to penicillin greater than 10 oxford units per cubic centimeter its resistance to streptomycin, aureomycin, chloromycetin and to sulfadiazine should be determined.

Treatment should not be initiated until the responsible organism or organisms have been identified and tested. It is best to obtain at least two positive cultures. While it is desirable to begin treatment as soon as possible the slight additional risk of delay will usually be more than offset by the essential therapeutic information gained from the culture and sensitivity studies. The only exceptions to the above rule are patients who are practically moribund and patients in whom the clinical diagnosis is unequivocal although multiple cultures of the blood have been negative. In the latter case cultures using increased carbon dioxide tension and anaerobic conditions should be utilized. Occasionally bloods drawn 5, 15 and 30 minutes after the subcutaneous administration of 0.5 cc of 1:1000 adrenalin will help in obtaining a positive culture. This procedure is contraindicated in patients with hypertension, coronary artery disease or severe congestive heart failure. Arterial blood and sternal marrow cultures may be positive when venous blood cultures are negative. Blood drawn during febrile periods is more likely to give positive results. Cultures should be incubated for at least 2 to 3 weeks before being called negative. Samples of positive cultures should be kept for the duration of the treatment.

First is the amount of penicillin needed for

day The second is how long should treatment be continued If continuously high penicillin plasma levels are maintained for a sufficiently prolonged time success will be achieved in a large majority of cases

The plasma penicillin level should be kept five to ten times higher than the in vitro sensitivity of the organism It has been shown that the minimal in vivo bacteriostatic level is at least four times the in vitro sensitivity The reason for this has not been clearly established Possibly the higher levels are needed to penetrate into the fibrin of the vegetative processes in order to inhibit the bacteria therein lodged It must be emphasized that the adequacy of blood levels can not be judged from the dosage required to clear the circulating blood of organisms This may be accomplished with inadequate doses and may not only fail to cure but may actually result in the development of a more resistant organism

In all cases of resistant organisms and in those cases that fail to achieve a negative culture in spite of having a penicillin plasma level at least five times the in vitro sensitivity of the organism help may be obtained from the following test based on the action of the patient's own serum during penicillin administration on the specific infectious organisms isolated It is similar to the test employed by Rammelkamp for the determination of in vitro sensitivity Two sets of tubes are used Samples of the patient's serum taken 5 minutes prior to the next penicillin injection are put in the tubes of both sets The first set is inoculated with 1:1000 dilution of a 6 hour broth culture of a standard strain of *Staphylococcus aureus* The second set of tubes is inoculated with a

large fluctuations in daily fluid intake Usually for each million units of crystalline

continuous intramuscular or intravenous drip If the intermittent intramuscular route is used and depending on the time interval between injections 1,500,000 to 2,000,000 units will be needed to obtain a plasma level of 10 oxford units per cubic centimeter With 1,000,000 units of crystalline penicillin a day variations occur so that a plasma level of only 0.5 oxford units per cubic centimeter may be obtained in a patient with normal renal function while if impaired renal function is present the plasma level may rise to 20 oxford units per cubic centimeter or more Regardless of how low the sensitivity may be the minimal total daily dose should be 600,000 units In those cases in which cultures have been repeatedly negative but in which the diagnosis has been satisfied by other criteria a minimum of 2,000,000 units of penicillin should be given per day This amount likewise should be used for the rare cases in which the general condition of the patient is too poor to await bacteriologic studies and the patient must have treatment immediately after admission to the hospital

METHODS OF ADMINISTRATION OF PENICILLIN Controversy has arisen in regard to the optimal method of administration of antibiotics With continuous intramuscular or intravenous therapy a more or less constant level may be expected With intermittent intramuscular injection the plasma level will vary depending on the time after injection that the test is run Only a small amount of penicillin will remain in the plasma 2 hours after a single intramuscular injection There has also been discussion as to whether it is

as closely as possible a continuous adequate level

If the total daily dose is not greater than 3,000,000 units the intermittent intramuscular route may be used Injections of $\frac{1}{4}$ the total daily dose should be given alternately in the buttocks and arms every 2 hours a day

diluent If no growth of the patient's organisms takes place in the undiluted tubes then an adequate penicillin plasma level is present If growth occurs in the undiluted tubes the level is insufficient and the amount of penicillin must be increased

As a rule one can estimate the plasma penicillin level by the amount of crystalline penicillin given This estimate will be altered if there is impaired renal function or sources of inactivation of penicillin and possibly by

SUBACUTE BACTERIAL ENDOCARDITIS

Until the introduction of penicillin the treatment of subacute bacterial endocarditis was inadequate and discouraging. It was estimated that at most 1 per cent of the cases had a spontaneous remission. With the advent of the sulfonamides the rate of cure rose to between 4 and 6 per cent. The use of the sulfonamides with heparin and with hyperthermia was said to result in a somewhat higher rate of recovery. However at best only 10 per cent of patients survived.

With the use of penicillin the outlook for these patients changed radically. As soon as adequate amounts of penicillin were available reports of cures began to appear in the literature in approximately 70 to 80 per cent of cases.

Etiologic Organisms. In the treatment of subacute bacterial endocarditis it soon became evident that the type of organism and its susceptibility to antibiotics were of the greatest importance. In the earlier cases most successful results were usually obtained when the organisms were extremely sensitive to penicillin. However it soon became apparent that resistant organisms could be adequately handled by using large amounts of penicillin.

Fortunately approximately 90 per cent of cases are caused by the alpha streptococcus (viridans). This organism is usually extremely sensitive to penicillin. Seven per cent of cases are caused either by the gamma streptococcus, the beta hemolytic streptococcus, the enterococci or a nonhemolytic streptococcus (the streptococcus s.b.e.). As a rule the organisms in this group are relatively insensitive. The remainder of cases have as their etiologic agent a gram negative bacillus such as the influenzal organism and a variety of other bacteria. These organisms are usually insensitive to penicillin but may be quite susceptible to streptomycin, to a sulfonamide, to aureomycin or chloromycetin.

Isolation and Determination of Characteristics of Organism. In treating subacute bacterial endocarditis the first step is culture of the organism or organisms involved. Occasionally in a particular case more than one organism is the cause of the disease. The sensitivity to penicillin must

be determined for all organisms. Of the various methods in use the serial dilution tests are probably as quick and as satisfactory in obtaining significant results with a minimum of errors. In each case a control is made with a standard strain of *Staphylococcus aureus* of known sensitivity (*Staphylococcus aureus* HMB 109). The usual bacteriostatic level of a penicillin sensitive organism is 0.01 to 0.1 oxford units per cubic centimeter. A range up to 1.0 oxford units per cubic centimeter is considered moderately sensitive. Anything above 1.0 must be considered relatively penicillin resistant. If the organism shows an in vitro sensitivity to penicillin greater than 1.0 oxford units per cubic centimeter its resistance to streptomycin, aureomycin, chloromycetin and to sulfadiazine should be determined.

Treatment should not be initiated until the responsible organism or organisms have been identified and tested. It is best to obtain at least two positive cultures. While it is desirable to begin treatment as soon as possible the slight additional risk of delay will usually be more than offset by the essential therapeutic information gained from the culture and sensitivity studies. The only exceptions to the above rule are patients who are practically moribund and patients in whom the clinical diagnosis is unequivocal although multiple cultures of the blood have been negative. In the latter case cultures using increased carbon dioxide tension and anaerobic conditions should be utilized. Occasionally bloods drawn 5, 15 and 30 minutes after the subcutaneous administration of 0.5 cc of 1:1000 adrenalin will help in obtaining a positive culture. This procedure is contraindicated in patients with hypertension, coronary artery disease or severe congestive heart failure. Arterial blood and sternal marrow cultures may be positive when venous blood cultures are negative. Blood drawn during febrile periods is more likely to give positive results. Cultures should

cultures should be made before the treatment.

Penicillin. There are two crucial problems to be answered in every penicillin treated case of subacute bacterial endocarditis. The first is the amount of penicillin needed per

day The second is how long should treatment be continued If continuously high penicillin plasma levels are maintained for a sufficiently prolonged time success will be achieved in a large majority of cases

The plasma penicillin level should be kept five to ten times higher than the in vitro sensitivity of the organism It has been shown that the minimal in vivo bacteriostatic level is at least four times the in vitro sensitivity The reason for this has not been clearly established Possibly the higher levels are needed to penetrate into the fibrin of the vegetative processes in order to inhibit the bacteria therein lodged It must be emphasized that the adequacy of blood levels can not be judged from the dosage required to clear the circulating blood of organisms This may be accomplished with inadequate doses and may not only fail to cure but may actually result in the development of a more resistant organism

In all cases of resistant organisms and in those cases that fail to achieve a negative culture in spite of having a penicillin plasma level at least five times the in vitro sensitivity of the organism help may be obtained from

employed by Rammelkamp for the determination of in vitro sensitivity Two sets of tubes are used Samples of the patient's serum taken 5 minutes prior to the next penicillin injection are put in the tubes of both sets The first set is inoculated with 1:1000 dilution of a 6 hour broth culture of a standard strain of *Staphylococcus aureus* The second set of tubes is inoculated with a broth culture of the patient's own organisms diluted to give approximately the same number of organisms per cubic centimeter of diluent If no growth is observed

penicillin must be increased

As a rule one can estimate the plasma penicillin level by the amount of crystalline

large fluctuations in daily fluid intake Usually for each million units of crystalline

continuous intramuscular or intravenous drip If the intermittent intramuscular route is used and depending on the time interval between injections 1,500,000 to 2,000,000 units will be needed to obtain a plasma level of 10 oxford units per cubic centimeter With 1,000,000 units of crystalline penicillin a day variations occur so that a plasma level of only 0.5 oxford units per cubic centimeter may be obtained in a patient with normal renal function while if impaired renal function is present the plasma level may rise to 20 oxford units per cubic centimeter or more Regardless of how low the sensitivity may be the minimal total daily dose should be 600,000 units In those cases in which cultures have been repeatedly negative but in which the diagnosis has been satisfied by other criteria a minimum of 2,000,000 units of penicillin should be given per day This amount likewise should be used for the rare cases in which the general condition of the patient is too poor to await bacteriologic studies and the patient must have treatment immediately after admission to the hospital

METHODS OF ADMINISTRATION OF PENICILLIN Controversy has arisen in regard to the optimal method of administration of antibiotics With continuous intramuscular or intravenous therapy a more or less constant level may be expected With intermittent

after a single intramuscular injection There has also been discussion as to whether it is

closely as possible a continuous adequate level

If the total daily dose is not greater than 3,000,000 units the intermittent intramuscular route may be used Injections of $\frac{1}{2}$ th the total daily dose should be given alternately in the buttocks and arms every 2 hours a day

and night. Hourly injections may be better but offer practical difficulties. If 5,000,000 or more units must be given per day, the continuous intravenous drip should be used. The total daily dose is dissolved in a liter of either 5 per cent glucose, normal saline, or Ringer's solution. Twenty to 40 milligrams of heparin should be added to the liter of solution in order to prevent clotting in the needle and to help avoid local thrombophlebitis at the sites of intravenous infusion. The rate of flow is adjusted so that the drip is fairly constant throughout the 24 hours. By this method it may be possible to keep one needle in a vein for 7 days or longer. If all accessible veins are thrombosed, or if for other reasons intravenous medication is impossible, the continuous intramuscular route may be used. However, myositis and fever are more likely to result when the intramuscular route is used. In cases extremely sensitive to penicillin, 600,000 units of a prolonged acting

not be used if the *in vitro* sensitivity of the organism is greater than 0.2 oxford units per cubic centimeter.

ENHANCEMENT OF PENICILLIN LEVELS * In cases requiring penicillin levels greater than 50 oxford units per cubic centimeter additional steps may be needed to obtain these values. Benzoic acid, diodrast, and para-aminohippuric acid have been used in the past. The latter two have the disadvantage of having to be given intravenously. Like wise in the large doses needed there have been some toxic effects. For the purpose of

nontoxic in the required doses and being effective when given orally.

It has been shown that 80 per cent of the urinary elimination of penicillin is by tubular excretion and 20 per cent is via glomerular filtration. Caronamide effectively blocks the tubular excretion of penicillin by inhibiting the mechanism responsible for the transport of penicillin by excretory tubular cells. Caronamide itself is eliminated by glomerular filtration. Thus, if large doses of penicillin alone do not result in the expected high plasma levels, or if levels are needed that cannot be reached with 10,000,000 units per day, the oral administration of caronamide is indicated. Because the duration of caronamide's action is 4 hours at most, it is necessary to give it orally at least every 8 hours. A dose of 3 gm. every 8 hours should result in a plasma caronamide level of between 20 to 30 mg. per cent. Usually this results in a threefold to fivefold increase in the plasma penicillin level. However, patients with some impairment of tubular function will need less caronamide to inhibit completely tubular excretion than will patients with normal tubular function. Slight nausea and vomiting may occur. This is not an indication for stopping the drug. Inasmuch as caronamide is precipitated in an acid urine one should maintain a high urinary output or an alkaline urine. Because of its relative lack of toxicity it may be given for periods up to 4 to 5 weeks. While caronamide is being administered urinary output and blood urea nitrogen should be checked to make certain that no gross alteration has occurred.

DURATION OF THERAPY The duration of treatment will vary from case to case. No objective tests are available to give a definite answer to this problem. Four weeks of continuous therapy is the minimum when the organism is sensitive to penicillin while 6 to 8 weeks is the usual length of treatment when one is dealing with a resistant organism. However, in all cases treatment should be continued for at least 3 weeks after subsidence of the patient's main symptoms and after the blood culture has become negative. While patients are being treated, blood cultures should be taken at least once a week. An antipenicillin agent (penicillinase) should be added to all blood cultures taken while the patient is on penicillin therapy.

adequate
Bc

This will help to inactivate the penicillin in the drawn plasma and thus aid in culturing any bacteria still present in the blood. Favorable therapeutic response is indicated by a return to normal of the temperature, pulse rate, gain in weight, an absence of sweats, the beginning recession of splenomegaly and

even in a patient who is responding favorably.

Nonspecific Supportive Therapy In addition to specific antibiotic therapy, supportive measures must also be employed. Thus, at the beginning of the treatment, if significant anemia is present, the patient should be given transfusions until a red count of 4,000,000 and hemoglobin of at least 75 per cent are obtained. In addition to the obvious benefit to the weakened myocardium, increase in antibody formation will

sorry vitamins must be administered if there are evidences of such deficiencies. If the patient's condition is such that adequate food intake is impossible, intravenous feedings

the usual manner. If congestive failure is present, digitalization and diuretics should be used as for any other patient. All foci of infection, especially infected teeth should be removed while the patient is undergoing treatment.

The Use of Streptomycin As mentioned earlier there are certain cases that do not

organism is either completely insensitive to penicillin or those which have failed for some reason to respond to maximal penicillin therapy. In such cases streptomycin sensitivity tests must be carried out.

The number of cases of streptomycin-treated subacute bacterial endocarditis is as yet too small to evaluate properly the in vitro tests of streptomycin sensitivity. However, if the sensitivity of the organism is 8 micro

on a regimen of at least 4 to 6 gm. of streptomycin per day. It should be given in divided intramuscular doses at 3 hour intervals. After a single intramuscular injection of streptomycin, relatively high plasma levels are present for approximately 4 hours. The drop in concentration is quite rapid after that period. It is essential that large doses of the drug be given from the start because bacteria have a great tendency to develop resistance to this antibiotic. Plasma levels should be obtained, as in cases treated with penicillin, and an attempt made to reach a level approximately five to ten times that of the in vitro sensitivity. After a favorable response treatment should be continued for 4 weeks.

Although toxic manifestations, both vestibular and auditory, are quite common when streptomycin is administered in large amounts over a relatively long period (2 to 3 weeks or more), a favorable result calls for the continuation of the drug for a total of at least 3 weeks in spite of these toxic manifestations. Audiometric and vestibular function tests should be done before treatment is started and at weekly intervals while therapy is being continued.

Aureomycin and Chloromycetin In the past few months, aureomycin and chloromycetin have been added to the field of antibiotics. While detailed reports of their use in bacterial endocarditis are yet to appear, they undoubtedly will be of aid in cases due to organisms poorly responsive to penicillin and streptomycin. Though these newer antibiotics may be effective against organisms known to be penicillin sensitive, their present use in bacterial endocarditis should be limited to those cases in which they are much more effective against the organism than either penicillin or streptomycin.

In general, aureomycin is more active against the coccal organisms than against gram negative bacilli. The hemophilus group particularly may be susceptible to aureomycin. Organisms such as penicillin resistant streptococci, pneumococci, and staphylococci should be tested for aureomycin sensitivity. Effectiveness has been demonstrated against *Brucella* and most *Salmonella*.

Dosage of aureomycin in cases of bacterial endocarditis is not settled. Administration by the oral route is preferred. It should be given every 4 hours. The sensitivity of the organisms should be determined and a dosage prescribed which will give a serum concentration of at least five times the *in vitro* sensitivity. Following an oral dose of 10 gm., serum concentration of 0.6 to 2.5 micrograms per cc. are obtained in 2 to 4 hours, and concentrations of 5 to 20 micrograms per cubic centimeter of serum are subsequently maintained during continuous oral administration of 1 gm. every 4 hours. The minimal amount of aureomycin in bacterial endocarditis should be 1 gm. every 4 hours. If *in vitro* sensitivity studies indicate need for greater amounts the dose may be increased to 2 gm. or more every 4 hours. Serious toxicity from aureomycin has not been reported. Gastric irritation which does occur, may be minimized by the administration of antacids or food. If the patient's condition precludes oral administration the intravenous route may be used. Aureomycin is given intravenously in a dosage one fifth that of the oral dose. At least 1 cc. of leucine diluent should be used for each 10 mg. of aureomycin. The sterile solution is injected immediately after preparation over a period of at least 5 minutes. Because of the frequency of thrombophlebitis, intravenous administration should be discontinued as soon as the patient is able to take the drug orally. Intramuscular therapy has been too painful for the prolonged administration of aureomycin.

Chloromycetin gives promise of success in the treatment of endocarditis due to *Brucella*, the *Salmonella* group, and the *coli* form bacteria. These groups though uncommon as a cause of endocarditis, have been among the most difficult to treat. Chloromycetin should be given orally as it is well absorbed from the gastrointestinal tract. The initial dose is approximately 50 mg. per kilogram of body weight. Following this 0.25 gm. should be administered every 3 hours. This schedule should result in a

tin. Serious toxic manifestations have not been observed.

With both aureomycin and chloromycetin the duration of treatment of bacterial endocarditis is still to be decided. However it is probable that treatment should be continued for at least 2 weeks after subsidence of the patient's main symptoms and sterilization of the blood stream. Although the potentialities of these newer antibiotics in the treatment of bacterial endocarditis are great it must be emphasized that our knowledge of their use is still in its infancy.

that the further valvular accumulation of leukocytes, fibrin, and organisms would be prevented. The subcutaneous administration of heparin is painful and the intravenous route is bothersome technically. While many of these objections have been overcome by the oral use of dicumarol subsequent experiences of numerous investigators have shown that patients do as well without the anti-coagulants which often complicate the treatment. Embolization has not been lessened by their use. Heparin frequently causes febrile reactions that may obscure the clinical picture. Hemorrhages have resulted and an occasional death has been attributed to these drugs. If thrombophlebitis or phlebothrombosis occurs as a complication during the treatment of subacute bacterial endocarditis routine heparin and dicumarol treatment should be instituted. Other than for these uses, anticoagulants have no place in the treatment of subacute bacterial endocarditis.

Relapses. Occasionally relapses may occur. This may be due either to an inadequate plasma level or to the early discontinuance

will kill the more sensitive of the organisms and yet allow certain less sensitive bacteria to multiply. The usual time for relapse is 2 to 4 weeks after the completion of the course.

Following completion of treatment and the patient should be carefully observed. The patient

greater than the usual dose of chloromycetin for organisms listed as susceptible to chloromycetin.

may be asymptomatic even though the culture is positive

In case of relapse the organism should again be tested for sensitivity and another complete course of treatment instituted. In other words it must be treated as a newly developed case of subacute bacterial endocarditis. It is preferable not to discharge a patient until 4 weeks after the antibiotics have been stopped. Careful follow up with frequent blood cultures should be continued for at least a year. Only then can the infection be considered arrested.

Complications The foremost complications during therapy are embolization and myocardial failure. Occasionally evidence of cerebral meningoencephalitis will be observed. Penicillin idiosyncrasy may be manifested by a rash or a febrile reaction. Usually this may be satisfactorily overcome by

In cases of infected emboli with abscess

acute bacterial endocarditis. Myocardial failure per se is not a complication of treatment. It may develop during or be a sequel to the infection. It is well known that in subacute bacterial endocarditis minute emboli, small infarcts and diffuse inflammatory reaction may be present in the myocardium. Structural alterations in the myocardium that occur with healing adequately explain the advent of failure. In cases where subacute bacterial endocarditis is superimposed on rheumatic heart disease a reactivation of rheumatic myocarditis frequently occurs. Likewise valvular damage may be increased during the processes of healing and further contribute to myocardial failure. The earlier the diagnosis of subacute bacterial endocarditis is made and treatment started the less likely is the occurrence of congestive failure. Digitalis, diuretics and a low salt diet should be used as in the treatment of any case of congestive heart failure.

Prophylaxis Perhaps one of the most important items is the prophylaxis of this disease. In all bacterial infections such as

pneumonias etc. blood cultures should be obtained before the institution of antibiotic therapy. This is imperative in all cases of previous valvular damage. In patients with known heart disease antibiotics must be given before all elective surgical procedures. Particularly important are tooth extraction which result in a 70 per cent incidence of transient bacteremia. Tonsillectomies, prosthetic operations, other genito-urinary procedures and any surgical intervention on infected tissues are apt to have subacute bacterial endocarditis as a sequel. Therefore it is recommended that such patients receive an injection of 600,000 units of a prolonged acting penicillin mixture. This dose should be given 2 to 3 hours before the procedure and daily for 2 to 3 days thereafter. In cases of subacute bacterial endocarditis undergoing therapy a careful search must be made for all foci of infection and their removal accomplished during the course of treatment.

The successful use of antibiotics has altered the views on surgery for cases of patent ductus arteriosus. Formerly one of the principal indications for ligation was the prevention of subacute bacterial endarteritis. At the present time it is felt that other sequelae such as failure of proper growth, progressive cardiac strain and disability and a dynamically large communication should be the determining factors rather than the prevention of endarteritis.

In active cases of subacute bacterial endocarditis the primary consideration should be the elimination of the infection by the use of antibiotics. Several months after the successful completion of such treatment ligation may be carried out as an elective procedure.

MILTON GROSSMAN
LOUIS N. KATZ

ACUTE BACTERIAL ENDOCARDITIS

In general results of treatment of acute bacterial endocarditis have been disappointing. Few reports of recovery have appeared in spite of availability of penicillin and streptomycin. It is hoped that the newer antibiotics— aureomycin and chloromycetin—will increase the survival rate in this disease. Accurate diagnosis at the earliest possible moment must be stressed. Acute endocarditis is characterized by its occurrence in a patient without previous known heart disease by its

short duration, and usually by its fulminating course. As a rule, the organisms responsible are the hemolytic streptococcus, the pneumococcus, and *Staphylococcus aureus*. In general, the treatment is similar to that of subacute bacterial endocarditis. However, one must not temporize even as much as with subacute bacterial endocarditis. Blood cultures and organism sensitivity should be obtained and therapy started immediately. The principles of therapy are the same as those of subacute bacterial endocarditis. Response to treatment should be evaluated within a few days and if a satisfactory result is not being obtained, either the dosage must be increased or an additional antibiotic be given.

MILTON GROSSMAN
LOUIS N KATZ

REFERENCES

Avery, N L, Jr, Mayer, O B, and Nelson, R C. Massive Doses of Penicillin in Treatment of Subacute Bacterial Endocarditis. *Ann Int Med*, 24: 900, 1946.

Beyer, K H, et al. Certain Pharmacologic Properties of 4' Carboxyphenylmethanesulfonamide (Caronamide), Including Its Effect on Renal Clearance of Compounds Other Than Penicillin. *J Pharmacol & Exper Therap*, 91: 272, 1947.

Beyer, K H, et al. Inhibitory Effect of Caronamide on Renal Elimination of Penicillin. *Am J Physiol*, 149: 355, 1947.

Beyer, K H, et al. Effect of Para aminohippuric Acid on Plasma Concentration of Penicillin in Man. *JAMA*, 126: 1007, 1944.

Boger, W P, et al. Caronamide, Compound that Inhibits Penicillin Excretion by Renal Tubules Applied to Treatment of Subacute Bacterial Endocarditis. *Am J M Sc*, 214: 493, 1947.

Buchbinder, W C, and Saphir, O. Heart Failure in Subacute Bacterial Endocarditis. *Arch Int Med*, 64: 336, 1939.

Crosson, J W, et al. Caronamide for Increasing Penicillin Plasma Concentrations in Man. *JAMA*, 134: 1528, 1947.

Dawson, M H, and Hunter, T H. Treatment of Subacute Bacterial Endocarditis with Penicillin, Second Report. *Ann Int Med*, 24: 170, 1946.

Dowling, H F, and Hursh, H L. Use of Penicillinase in Cultures of Body Fluids Obtained from Patients under Treatment with Penicillin. *Am J M Sc*, 210: 756, 1945.

Favour, C B, et al. Progress in Treatment of Subacute Bacterial Endocarditis. *New England J Med*, 234: 71, 1946.

Fiese, M J. Cardiac Failure in Penicillin Treated Subacute Bacterial Endocarditis. *Arch Int Med*, 79: 436, 1947.

Fleming, A. In Vitro Tests of Penicillin Potency. *Lancet*, 1: 732, 1942.

Flippin, H F, et al. Penicillin in Treatment of Subacute Bacterial Endocarditis, Preliminary Report on 20 Cases Treated Over One Year Ago. *JAMA*, 129: 841, 1945.

Geiger, A J, and Goerner, J R. Treatment of Subacute Bacterial Endocarditis with Penicillin in Peanut Oil and Beeswax. *New England J Med*, 235: 285, 1946.

Gerber, I E, Schwartzman, G, and Baehr, G. Penetration of Penicillin into Foci of Infection. *JAMA*, 130: 761, 1946.

Glaser, R J, et al. Effect of Penicillin on Bacteremia Following Dental Extraction. *Am J Med*, 4: 55, 1948.

Grossman, M, et al. Treatment of Subacute Endocarditis Due to Organisms Highly Resistant to Penicillin, Case Report. *Am Heart J*, 34: 592, 1947.

Honigman, A H, and Kams, J R. Herled Subacute Bacterial Endocarditis, Report of 2 Cases with Death Due to Congestive Heart Failure. *Ann Int Med*, 26: 704, 1947.

Hunter, T H. Use of Streptomycin in Treatment of Bacterial Endocarditis. *Am J Med*, 2: 436, 1947.

Hunter, T H. Treatment of Subacute Bacterial Endocarditis with Antibiotics. *Am J Med*, 1: 83, 1946.

Hunter, T H, and Duane, R B, Jr. Subacute Bacterial Endocarditis Due to Gram negative Organisms. *JAMA*, 132: 209, 1946.

Loewe, L, and Altme, Werber, E. Clinical Manifestations of Subacute Bacterial Endocarditis Caused by Streptococcus s b e. *Am J Med*, 1: 353, 1946.

Loewe, L, and Eiber, H. Subacute Bacterial Endocarditis of Undetermined Etiology. *Am Heart J*, 34: 349, 1947.

Loewe, L, et al. Streptococcus s b e in Subacute Bacterial Endocarditis. *JAMA*, 130: 257, 1946.

Loewe, L, et al. Superiority of Continuous Intravenous Drip for Maintenance of Effectual Serum Levels of Penicillin, Comparative Studies with Particular Reference to Fractional and Continuous Intramuscular Administration. *J Lab & Clin Med*, 30: 730, 1945.

MacLean, H, and Howell, K M. Two Coexistent Strains of Viridans Streptococcus Isolated from Blood Cultures by Penicillin Sensitivity Tests. *Am J M Sc*, 214: 53, 1947.

Mokotoff, R, et al. Treatment of Bacterial Endocarditis. Unpublished.

Nath, S. Soc.

Priest, W S, and McGee, C J. Streptomycin in Treatment of Subacute Bacterial Endocarditis, Report of 3 Cases. *JAMA*, 132: 124, 1946.

Rammellamp, C H. Method for Determining Concentration of Penicillin in Body Fluids and Exudates. *Proc Soc Exper Biol & Med*, 51: 95, 1942.

Schlichter, J G, and MacLean, H. Method of Determining Effective Therapeutic Level in Treatment of Subacute Bacterial Endocarditis with

- Penicillin Preliminary Report *Am Heart J* 34
209 1947
- Scudder S T and Deputy R Acute Bacterial
Endocarditis Penicillin resistant *Streptococcus*
haemolyticus *Northwest Med* 46 599 1947
- Sesbury J H Subacute Bacterial Endocarditis
Experiences During Past Decade *Arch Int Med*
79 1 1947
- Shaw C C et al Enhancement of Penicillin Blood
Levels in Man by Means of New Compound
Caronamide *Am J Med* 3 206 1947
- Thill C J and Meyer O O Experiences with
Penicillin and Dicumarol in Treatment of Sub
acute Bacterial Endocarditis *Am J Med Sc* 218
800 1947

- 1948
- Wilhelm F et al Treatment of Acute Bacterial
Endocarditis with Penicillin *Ann Int Med* 26
221 1947

ACUTE MYOCARDITIS OF INFECTIOUS DISEASE

Modern clinicians are becoming increasingly aware of the fact that acute infections other than rheumatic fever and diphtheria are capable of producing acute myocarditis. Recent contributions to the medical literature emphasize that cardiac manifestations of acute infectious diseases occur more frequently than are commonly recognized. Mild infections of the upper respiratory tract such as nasopharyngitis and tonsillitis may produce an acute inflammation of the myocardium which unless carefully sought may escape detection. Frequently the cardiac symptoms and findings do not appear until the primary disease has subsided so that once the diagnosis is established treatment must be directed primarily toward the heart.

The patient must be kept at absolute bed rest until all signs of active infection within the heart have been absent for one week. Before any activity is allowed the temperature, pulse rate and blood pressure should be normal. The electrocardiogram, leukocyte count and sedimentation rate of the red blood cells also must be within normal limits. Once the decision is made to allow the patient out of bed activity must be increased gradually as in any other situation in which the heart has suffered an acute insult. All laboratory work should be rechecked

at the end of one week of activity and if evidence of reactivation of the inflammatory process appears bed rest must be continued for a longer period.

If heart failure occurs the usual treatment for cardiac decompensation must be instituted including the use of digitalis, oxygen, proper fluid balance and a low sodium diet.

cutaneous
the
ade

quately

FRANKLIN A. KYSER

REFERENCES

- Candel S and Wheelock M C Acute Nonspecific
Myocarditis *Ann Int Med* 23 309 1945
- Carr J C and Walsh J A Acute Infectious Myo-
carditis *Illinois M J* 65 184 1934
- Gore I and Saphir O Myocarditis Associated
with Acute Nasopharyngitis and Acute Tonsil-
litis *Am Heart J* 34 831 1947
- Saphir O Myocarditis: General Review with
Analysis of Cases *Arch Path* 32 1000 1941

CHRONIC VALVULAR DISEASE

A discussion of the management of the patient with chronic valvular disease must be confined to general principles rather than specific suggestions since the complications of valvular heart disease usually bring the patient to the physician rather than the valve lesion per se. Since complications such as congestive heart failure, arrhythmias and bacterial endocarditis are discussed elsewhere in this book no attempt will be made to include the management of these problems in this discussion.

The major consideration in any individual with known valvular disease is to prevent the development of a cardiac neurosis and to keep the patient in a state of mind in which he considers himself to be a useful member of society. Certainly he should be informed that he has a cardiac lesion for only by the knowledge of this fact can he help himself to avoid future difficulty. The physician must truly practice the art of medicine when imposing necessary restrictions. An attitude of reassurance and optimism to the patient are of prime importance. In the absence of heart failure it is usually unnecessary to limit normal physical activity. Strenuous exercise

gardening may be advised for recreation. In children normal gymnasium classwork should be permitted whenever possible unless extensive heart damage is present. Need less to state every case must be individualized depending on the specific problem involved.

The patient must be warned that infections of any type should be treated with respect in order to prevent recurrence of rheumatic fever or the development of bacterial endocarditis. The importance of preoperative treatment with penicillin or aureomycin even with such a minor procedure as dental extraction should be emphasized. It is wise to caution against excesses of any kind especially with regard to gain in weight and unusual fatigue. Great effort must be made by the physician to instruct the patient how to live within his restrictions. Certainly with wise counsel and modern therapeutic weapons the patient with chronic valvular disease may expect greater longevity than was thought possible in the years that have passed.

The mere presence of a valvular lesion should not be considered a contraindication to pregnancy or to a surgical procedure that may make life more comfortable. All too often these patients are denied the benefits of surgery or the happiness of raising children merely because a heart murmur is present.

In all patients with valvular disease periodic examinations are desirable in order that the early development of any complication may be noted. Careful observation and judicious treatment will aid many patients with organic heart disease to live long and useful lives.

FRANKLIN A. KISER

PERICARDITIS

Pericardial disease may occur as an isolated entity as a part of acute heart disease or secondary to a systemic illness. It is a not uncommon condition as is shown by the survey of Smith and Williams in which they found postmortem evidence of pericarditis in 4 per cent of over 8000 cases at necropsy.

White states that evidence of pericarditis is found in about 5 per cent of necropsy examinations.

Acute Pericarditis Acute pericardial disease occurs most commonly as the result of rheumatic fever and in certain infectious diseases as pneumonia, influenza and tuberculosis. The pericarditis resulting from acute myocardial infarction and uremia will not be discussed in this section.

The treatment of acute pericarditis must of necessity depend on the causative disease. If an acute systemic infection is present such as pneumonia or meningitis, penicillin, streptomycin or one of the sulfonamides must be employed depending on the specific organism involved. If rheumatic fever is the cause the usual therapeutic measures for this condition are indicated.

For relief of pain, morphine $\frac{1}{4}$ grain (15 mg.) or codeine $\frac{1}{4}$ grain (30 mg.) or salicylates 15 grains (1 gm.) may be used to control the pain. Bed rest must be enforced until all evidence of pericardial involvement has subsided. An ice pack over the precordium may aid in keeping the patient comfortable. Barnes and Burchill have pointed out that acute nonspecific pericarditis following upper respiratory tract infections may simulate acute myocardial infarction. In these patients diagnosis is often difficult and they must be treated with bed rest until the electrocardiogram returns to normal. The prognosis in this type of pericarditis is excellent as compared to the outlook in coronary thrombosis.

The course of acute pericarditis must be carefully observed for signs of the development of fluid in the pericardial sac. The appearance of an effusion need not be cause for alarm unless signs of a rise in venous pressure and fall in arterial pressure occur. If these findings which indicate a very high intrapericardial pressure become apparent then tapping of the pericardial sac should be carried out.

The best location to try the tap is usually in the fifth intercostal space just inside the outer border of percussion dullness. The skin should be thoroughly cleansed and anesthetized with 2 or 3 cc. of 0.5 per cent novocain solution. The exploring needle should be inserted slowly between the ribs

pointing slightly inward toward the spinal column. As the needle enters the pericardial sac a sense of resistance will be noted. If the needle moves with the contraction of the heart it should be slightly withdrawn. Fluid may then be easily aspirated if it is a serous effusion. If this attempt is not successful the needle should be withdrawn and the same procedure repeated in the fourth intercostal space slightly closer to the left sternal border. As much fluid as is possible may be removed without ill effect. The introduction of a small amount of air, 50 to 100 cc. into the pericardial sac may prevent the development of adhesions, but this is not advisable as a routine procedure. The entire operation must be carried out with strict aseptic precautions.

It is usually not necessary to tap the pericardial sac more than once, but in extreme cases paracentesis may be repeated every 4

LOW OF PERICARDIAL FLUID

If it is suspected that a purulent fluid is present a large trocar should be used for aspiration. It is imperative that drainage be adequate and in most cases incision and drainage is necessary. The introduction of penicillin or streptomycin into the pericardial sac each time aspiration is carried out is of definite value when susceptible organisms are the etiologic agent. If after two or three injections of an antibiotic no improvement occurs then pericardiostomy must be done. Fatalities may result from withholding surgical drainage in a patient who does not improve with conservative management. The administration of parenteral antibiotic therapy must be carried out in all cases of purulent pericarditis.

Chronic Constrictive Pericarditis. The only important form of chronic pericarditis from the therapeutic standpoint is constrictive pericarditis. In this condition the heart is encased in a dense covering of adhesions and in some cases deposits of calcium may be present. This encasement of the heart prevents adequate diastolic filling and results in a diminished cardiac output and marked elevation of the venous pressure. The only way to correct such a condition is to free the heart of this mechanical burden by

resection of the pericardium. Before operation is attempted adequate preoperative preparation is imperative. The patient must follow a low sodium, high protein diet. All abnormal collections of fluid should be removed from the body by use of ammonium chloride, 15 grams (1 gm.) four times daily, and mercurial diuretics. Thoracentesis and paracentesis may be necessary in order to relieve hydrothorax and ascites. Digitalis is seldom indicated in constrictive pericarditis unless it be to slow the rate of auricular fibrillation. If this arrhythmia is present the risk of surgery is greatly increased.

Careful evaluation of hepatic function is desirable preoperatively. If extensive liver damage has resulted from prolonged passive congestion the prognosis is much less favorable than in the individual who shows little evidence of impaired hepatic function.

Postoperatively the administration of oxygen by mask or tent is imperative. Sodium restriction in the diet and in parenterally administered fluids is important. The use of mercurial diuretics may be necessary to aid in elimination of recurrent edema. Digitalis may be of value following operation to restore compensation to a myocardium that shows signs of failure as a result of the surgical procedure.

In some patients dramatic results may appear within several days following operation. If however the disease is of long standing as is usually the case 6 months to a year may be necessary before full benefit of the surgical procedure is obtained.

FRANKLIN A. KYSER

REFERENCES

- Barnes A. R. and Burchell H. B.: Acute Pericarditis Simulating Acute Coronary Occlusion. Report of 14 Cases. *Am Heart J* 23:247 1942.
- Blalock A. and Burwell C. S.: Chronic Pericardial Effusion. Report of 23 Cases of Constrictive Pericarditis. *Surg Gynec & Obst* 73:433 1941.
- Boas M. F. and Ellenberg M.: Rheumatic Pericarditis with Effusion Treated with Salicylates. *JAMA* 115:345 1940.
- Burwell C. S. and Ayer C. M.: Constrictive Pleuritis and Pericarditis. *Am Heart J* 22:267 1941.
- Camp P. D. and White P. M.: Pericardial Effusion. Clinical Study. *Am J Med Sci* 184:782 1932.
- Grossman C. M.: Pneumococcal Pericarditis Treated with Intrapericardial Penicillin. Report of a Case. *New England J Med* 233:689 1945.

Smith H L and Wilkus F A Pericarditis
Chronic Adherent Pericarditis *Arch Int Med*,
50 171 1932

White P D *Heart Disease* New York The Mac-
millan Company, 1914

HEART DISEASE IN PREGNANCY

Prenatal Considerations The management of the pregnant patient with organic heart disease requires keen judgment and careful observation for the 9 month period of the pregnancy and often well into the puerperium. There must be co operation between the obstetrician and internist or cardiologist if the optimal results in reducing maternal and infant morbidity and mortality are to be attained.

Certain routine precautions must be observed more rigidly in the pregnant cardiac patient than in an otherwise normal pregnant woman. Fatigue must be avoided at all costs, and long shopping trips or excessive exercise is forbidden. Upper respiratory tract infections must be treated with great care and obesity avoided. Anemia must be prevented or corrected with adequate medication.

A thorough understanding of the changes that occur in the circulation during pregnancy is essential for the efficient management of the pregnant patient with heart disease. For this reason a brief résumé of physiologic principles is included here.

Cardiac output, blood volume, and velocity of blood flow increase during pregnancy. Many observations indicate that the maximal load is reached early in the eighth month and during this period the work of the heart is increased approximately 50 per cent. During the ninth month however, heart failure may appear for the first time, as emphasized by Dunum and Rubricus, so that the last lunar month is not without danger.

By far the most common type of cardiac disability found in the pregnant woman is rheumatic heart disease. It must be emphasized that the mere presence of a cardiac lesion should not be the cause for alarm. It is always cause for careful and frequent observation of the patient. Many individuals with cardiac damage go through pregnancy uneventfully and deliver normal babies. Certainly the mere presence of organic heart disease should not be considered as cause for therapeutic abortion. The most important

factor to be evaluated is the functional efficiency of the heart, the history or presence of congestive heart failure must be considered as a signal of impending danger in the pregnant woman. If a history of cardiac failure is obtained, it is unlikely that the heart will stand the burden that pregnancy demands and interruption is advisable. Throughout the prenatal period the patient should be examined every 7 to 14 days. Persistent rales at the bases of the lungs, dyspnea, and cough herald the onset of congestive failure. If these signs appear during the first 6 months, the patient must be put to bed and the cardiac efficiency restored to the best possible state. When the patient is in satisfactory condition, interruption of the pregnancy should be carried out by abdominal hysterotomy. If the onset of decompensation is delayed beyond 6 months the patient should be confined to bed and managed by the usual methods of treatment for cardiac failure.

Bed rest must be enforced until spontaneous labor occurs. Delivery is best carried out with the aid of an episiotomy and low forceps. Even if compensation is not restored it is unwise to add the burden of any operative procedure to the failing heart. Hamilton and Thompson point out that the mortality rate in their series was four times greater with abdominal than pelvic delivery. Manipulative maneuvers must be avoided unless absolutely indicated from the obstetrical standpoint.

The presence of auricular fibrillation, like that of heart failure, must be cause for concern. If chronic fibrillation is present, it is wise, when possible, to avoid pregnancy. The onset of this arrhythmia during early pregnancy is an indication for abortion. During the first trimester, bed rest and digitalis or quinidine, when the heart rate is rapid may succeed in carrying the patient successfully to term.

Anesthesia More important than the anesthetic itself is the method of administration. Whenever possible, a person trained in anesthesia should be present during the delivery of the child. Ether, by the open drop method or, if the closed system is employed with liberal amounts of oxygen is well tolerated by the cardiac patient. Nitrous oxide and oxygen should be avoided because of the

danger of asphyxia Spinal anesthesia may be used provided a drop in blood pressure is prevented

Postnatal Consideration It is unusual for the heart to fail for the first time or for failure to recur after delivery If heart failure does appear during the puerperium, one should suspect the presence of a complication such as embolism, atelectasis, or shock It is wise to keep the patient in bed for 2 to 3 weeks following delivery in order to allow the circulatory changes to return more fully to normal Lactation is not harmful to the cardiac patient

FRANKLIN A KYSER

REFERENCES

- Bunim, J J and Rubincius J Determination of Prognosis of Pregnancy in Rheumatic Heart Disease *Am Heart J*, 35 282 1948
Gorenberg, H, and McGleary J Rheumatic Heart Disease in Pregnancy *Am J Obst & Gynec* 41 44 1941
Hamilton B E, and Kellogg F S Cardiac Disease in Pregnancy Prognosis Medical and Obstetric Handling *JAMA* 91 1942 1928
Hamilton, B E and Thomson K J *Heart in Pregnancy and the Child Bearing Age*, with a Section entitled Delivery and Obstetrical After

efficiency of the heart Studies of the circulation time, vital capacity, and venous pressure should be carried out when necessary

The mere presence of organic heart disease need not be cause for alarm Any patient who is capable of carrying on his normal daily activities without distress will tolerate an operation with little difficulty All too often, individuals are denied the comfort or increased life expectancy which well chosen operations may offer merely because of the existence of a heart murmur or evidence of cardiac enlargement A carefully performed operation adds no more load to the circulation than the daily activities of the patient However, in many patients with heart disease, certain factors exist which greatly increase the risk of surgery, and in these individuals careful judgment and expert treatment are imperative if the patient is to survive

Congestive heart failure should be relieved before any operative procedure is attempted unless an extreme emergency exists The use of rest, digitalis, diuretics, and dietary restriction of sodium will hasten the restoration of compensation It is wise to have the patient

- Stroud W D (Editor) *The Diagnosis and Treatment of Cardiovascular Disease* Philadelphia F A Davis Company, 1945
White P M *Heart Disease* New York The Macmillan Company 1944

HEART DISEASE IN THE SURGICAL PATIENT

With present advances in anesthesia, chemotherapy, antibiotics, and knowledge of fluid balance, the cardiac patient need not be denied necessary surgical intervention Careful preoperative preparation may convert a poor surgical risk into a satisfactory candidate for the surgeon's scalpel

A careful cardiac history and physical examination are of prime importance in the preoperative evaluation In addition to the usual laboratory procedures, a roentgenographic examination of the chest and an electrocardiogram must be made No effort should be spared to determine the functional

After full digitalization, it is wise to continue maintenance dosage of digitalis and this drug may have to be administered parenterally during the first few days following operation Oral food and fluid intake should be encouraged as soon as possible and care must be taken not to overload the circulation with excessive amounts of intravenous fluids Usually 2500 cc of fluid will adequately satisfy the need for water and if this amount is administered slowly, no grave results will ensue The use of oxygen postoperatively is of great benefit to the failing heart and its routine administration for the first 24 hours postoperatively may be of definite value Deep breathing and frequent moving must be encouraged to prevent pulmonary complications and early ambulation is advisable when possible

A major problem requiring careful judgment is the patient with coronary artery disease Certainly no person with evidence of a recent myocardial infarction should be op-

erated on until a minimal period of 8 weeks has elapsed. Operation should be postponed even longer whenever feasible. The presence of angina pectoris is an ominous sign and when this condition exists elective surgery should be avoided. Unfortunately many older individuals with definite coronary atherosclerosis require operations and in these patients surgery must be carried out despite the increased risk. Vasodilators such as aminophylline 3½ grains (0.25 gm) administered intravenously or 7½ grains (0.5 gm) intramuscularly may be of slight value in increasing the coronary circulation preoperatively and postoperatively. More important however than drug treatment is careful administration of a well chosen anesthetic and the avoidance of drops in blood pressure and shocklike states. Prostatic operations usually because of the age group in which they are necessary may precipitate coronary thrombosis and in these patients sudden drops of blood pressure may prove fatal (Master, Dack and Jaffe, Kretschmer and Butler).

The presence of auricular fibrillation increases the risk of surgery, especially in pa-

in non fibrillators to 22.2 per cent in patients with this arrhythmia in which rheumatic heart disease was the etiologic factor. Sprague also emphasizes that auricular fibrillation in the arteriosclerotic individual is not nearly as grave a sign as in the rheumatic

the drug of choice. If quinidine is used it should be administered in a dose of 8 grains (0.2 gm) four times daily for the first day and if this dose does not control the arrhythmia the drug may be increased to 0.2 gm every 2 to 3 hours. If any symptoms of idiosyncrasy become apparent quinidine should be discontinued. In patients suffering from hyperthyroidism the presence of auricular fibrillation need not be cause for alarm provided adequate preoperative preparation of the metabolic state was adequate. More often than not the heart condition will actually be improved by subtotal thyroidectomy. The use of antithyroid drugs such as 6 propyl thiouracil

may supplant the need of surgery in extreme cases in which the risk of operation is high.

Chronic valvular disease does not greatly increase the surgical risk if heart failure or an arrhythmia is not present. It is exceedingly important however that all such patients be adequately treated with penicillin or aureomycin before and after surgery to prevent the development of a valvular infection. Subacute bacterial endocarditis may result from a minor procedure as a dental extraction and antibiotic or chemotherapy greatly reduces the danger of this complication.

In addition to the above problems certain general considerations should be mentioned. Obesity increases the risk of postoperative complications in any patient and especially in cardiac patients. Whenever possible adequate weight reduction should be enforced before any elective surgical procedure is attempted.

Infection should be controlled at all times with properly chosen drugs and whenever possible the causative organism should be accurately identified in order to determine the most effective agent for its eradication.

Postoperative dilatation of the stomach or gaseous distention of the bowel may hamper normal respiratory effort and these complications must be treated as soon as their appearance is observed.

The choice of anesthetic for the cardiac patient must be made with care and when possible the aid of a trained anesthetist should be sought. Adequate sedation preoperatively is of great value in allaying the anxiety of the patient and in facilitating the induction of the general anesthetic. Cardiac patients tolerate ether well. Sodium pentothal

heart failure spinal anesthesia may be used provided all precautions to prevent drops in blood pressure are observed. Cyclopropane must be administered only by one thoroughly familiar with its use. This agent may produce abnormalities of cardiac rhythm and for this reason its value is limited. During the administration of any anesthetic, anoxia and violent muscular contractions must be avoided.

FRANKLIN A. KYSER

REFERENCES

Belinkoff, H. Choice of Anesthesia in Cardiac Dis-

ment of the already damaged heart The development of cardiac failure requires the usual treatment, as described elsewhere in this book

FRANKLIN A KYSER

REFERENCES

1415, 1938
Sprague, H B Heart in Surgery, Analysis of Results of Surgery on Cardiac Patients during Past 10 Years at Massachusetts General Hospital Surg, Gynec & Obst, 43 54, 1929
Stroud, W D (Editor) *Diagnosis and Treatment of Cardiovascular Disease* Philadelphia F A Davis Company, 1945
White P D *Heart Disease* New York The Macmillan Company, 1944

Beck, C S Contusions of Heart JAMA, 104 109 1935

Stroud, W D (Editor) *Diagnosis and Treatment of Cardiovascular Disease* Philadelphia F A Davis Company, 1945
Stern R A *Trauma In Internal Disease* New York Grune & Stratton, 1945

CARDIAC TRAUMA

The diagnosis of injury to the heart is

CARDIAC DECOMPENSATION

to any part of the body, provided it is of sufficient violence, and its force is transmissible to the heart," emphasizes the necessity of careful cardiac examination in any injured person It is possible for a variety of injuries to occur such as penetrating wounds, rupture of the valves or septum, rents in the endocardium and hematoma formation or contusion of the muscular wall

Once the diagnosis of a cardiac injury is made, the patient should be kept at absolute bed rest and if signs of cardiac tamponade appear, immediate surgical intervention should be attempted Morphine may be used freely and the usual measures to combat shock should be instituted If abnormal rhythm is present, quinidine, 3 grams (0.2 gm), four times daily may prevent the development of ventricular fibrillation

In contusions of the heart muscle absolute bed rest should be maintained for a minimum period of 6 weeks An angular type of pain may be present resulting from injury to the coronary arteries Frequent electrocardiograms should be made in order to follow carefully the progress of the cardiac lesion When the patient is allowed out of bed, the return to activity must be slow and graduated

If evidence of pericardial effusion becomes apparent, it is wise to remove the pericardial fluid in order to prevent further embarrass-

ment of the already damaged heart The development of cardiac failure requires the usual treatment, as described elsewhere in this book

Normally the work of the heart may be increased within wide limits without the production of undue symptoms During severe muscular exercise the cardiac output may increase as much as 900 per cent of the resting value In sedentary individuals this range of increase is much less than in those accustomed to strenuous physical work The range of normal response to exercise varies considerably in different persons, it tends to decrease gradually as the individual grows older Broadly speaking, heart failure may be said to occur when there is curtailment of the remarkably broad power of accommodation of the heart to the ever varying demands of the organism Evidence of heart failure is manifested by certain symptoms shortness of breath on exertion and even at rest, easy fatigue on effort, precordial discomfort, and certain signs, e.g., breathlessness, orthopnea, dyspnea, cyanosis, pulmonary rales, pleural effusion, distention of veins and increased venous pressure, congestion of the liver, ascites, and edema of the lower extremities

We shall confine our remarks to the subject of backward failure, that is, heart failure involving the left heart, the right heart, and a combination of both In left heart failure, the manifestations are observed particularly in the lungs and consist of a low-

liver, increased venous pressure, ascites, and edema of the lower extremities The symp-

toms and signs of heart failure may be simulated by those of other conditions especially pulmonary disease anemia bronchogenic and peritoneal carcinoma cirrhosis of the liver avitaminosis and other acute or chronic ailments

Factors Inducing Heart Failure Before discussing the treatment of heart failure in detail it is well to mention the factors responsible for the induction of the heart failure since an appreciation of these factors will result in more intelligent and adequate therapy (1) Increased work Under this heading may be placed thyrotoxicosis arrhythmias with rapid ventricular rate valvular lesions hypertension arteriovenous fistula and pregnancy (2) Impaired nutrition of the heart Under this category may be mentioned anemias of various types coronary disease and malnutrition (3) Pulmonary heart disease This includes pulmonary arteriosclerosis pulmonary fibrosis pulmonary emphysema and the end results of multiple pulmonary emboli (4) Inflammatory heart disease The most common types are rheumatic myocarditis associated with subacute bacterial endocarditis diphtheritic idiopathic type of interstitial myocarditis and virus infections (5) Degenerative This includes coronary artery disease with myocardial fibrosis fatty degeneration and amyloid disease (6) Avitaminosis Beriberi is the most important type (7) Extrinsic This includes pericardial effusion and pericardial adhesions (8) Various combinations of the above

Methods of Treatment The treatment of heart failure will be discussed under the following headings (1) rest of the heart (2) treatment of cardiac edema (3) treatment of acute left heart failure (4) surgical measures and (5) other methods of therapy (chemotherapy treatment for impaired nutrition altered metabolic states electrolyte changes and climate)

Rest of the Heart Rest of the heart may be divided into two categories (1) bed rest and (2) decrease of cardiac work while the patient is resting in bed

BED REST The importance of bed rest in the treatment of heart failure cannot be overemphasized Bed rest not only reduces the work of the heart to a minimum but

decreases the metabolic demands of the tissues for blood The value of bed rest is not as equally applicable to left as to right heart failure In left heart failure the period of bed rest in some patients may be curtailed to about 1 or 2 days thereafter the patient frequently does better by sitting in a chair which causes a considerable amount of fluid to gravitate to the lower portions of the body thus diminishing the strain on the heart In the presence of right heart failure bed rest may be prolonged to 2 or 3 weeks depending on the individual case Recent knowledge relating to the abuse of bed rest is important in this connection This is particularly applicable to patients with heart disease especially in the older age groups Some of the deleterious effects of bed rest are tendency to develop hypostatic congestion of the lungs and pneumonia phlebothrombosis with pulmonary infarction and occasionally arterial thrombosis Patients with phlebothrombosis and patients above the age of 50 should be encouraged to exercise their arms and legs and to move around in bed and be allowed out of bed as soon as their condition permits The use of anticoagulants as a prophylactic measure against development of vascular occlusion in such patients and particularly those with auricular fibrillation is gaining more popularity

LOW CALORIE DIET A low calorie diet 800 to 1000 calories reduces the work of the heart by reduction of the metabolic rate which may drop to -20 or -30 Obesity is an additional indication for weight reduction Obesity involves an added strain on

function Frequently a loss of weight down to the optimal range may not only improve the exercise powers of the patient but may postpone for years the onset of heart failure

THIOURACIL Thiouracil acts by reducing the basal metabolic rate its use depending on physiologic principles similar to those mentioned under thyroidectomy Propyl thiouracil which is less toxic than thiouracil has been tried in occasional patients with heart failure unassociated with thyroid toxicity as well as those with thyrotoxicosis its

use however has not gained much popularity

TREATMENT OF RAPID RATE The occurrence of an arrhythmia with a rapid ventricular rate results in myocardial exhaustion owing to the abbreviation of the diastolic rest period of the heart. A rapid ventricular rate if sufficiently prolonged may induce heart failure even in a normal heart; this occurs with greater ease in an already damaged heart. A rapid ventricular rate associated with auricular flutter or auricular fibrillation responds to digitalis. Auricular paroxysmal tachycardia may be abolished by carotid sinus pressure by prostigmine plus carotid sinus pressure by digitalization or by the administration of quinidine. Nodal tachycardia yields to similar therapeutic measures. Ventricular paroxysmal tachycardia can usually be abolished by quinidine.

Treatment of Edema The underlying principles of the treatment of edema of cardiac origin consist of (1) the administration of the mercurial diuretics (2) digitalization (3) restriction of sodium with fluid intake limited to 1200 to 2500 cc per day (4) mechanical removal of the effusion.

The extracellular fluid may increase by 50 per cent before actual edema becomes evident. In this stage of "preclinical decompensation" as emphasized by Christian many years ago there may be symptoms of breathlessness, fatigue and slight swelling of the ankles toward evening. This stage may last for many years before manifest heart failure is evident. Such patients are markedly improved by the regimen outlined for the treatment of heart failure.

DIURETICS The use of the mercurial diuretics is probably the most important single method employed in the treatment of heart failure. These act by preventing the reabsorption of sodium by the renal tubules; considerable amounts of sodium are therefore eliminated in the urine and large amounts of water are carried off with this electrolyte. This diuretic may be given intravenously, intramuscularly, subcutaneously, rectally or by mouth.* It is about equally

efficacious when it is given intravenously or intramuscularly. The oral administration of mercurial diuretics has the following disadvantages: (1) it is less effective than the intramuscular or intravenous route; (2) it often produces gastric irritation; (3) occasionally it tends to produce toxic renal effects; (4) it occasionally produces an ulcerative stomatitis (this rarely occurs with the parenteral methods). Rectal administration of mercurial diuretics while efficacious is not desirable because it frequently produces a proctitis.

Relatively few contraindications to the administration of the mercurial diuretics exist. In the presence of heart failure they may be given even when a cloud of albumin is present in the urine and with mild to moderate degrees of azotemia. They have occasionally

chief contraindications to their use are in acute glomerulonephritis and marked grades of azotemia which are considered to be the result of primary renal disease and not the result of congestive failure.

The patient should be weighed on admission and daily during the administration of the diuretic. The frequency of its administration in the initial stages of congestive failure is as follows: an initial dose of 0.5 to 1 cc may be given intramuscularly and this may be repeated daily until a considerable amount of fluid is removed. Thereafter the dose may be given every other day or every third day until that stage is reached when most of the extracellular fluid has been removed. The patient is then put on a maintenance dose which may be given every one or two weeks as indicated.

The favorable effects of this drug consist in a marked diuresis which may reach as much as 6000 to 7000 cc following a single injection. A patient may lose as much as 10 lbs of body weight with a single dose with no untoward symptoms and with considerable improvement; however, relatively little or moderate diuresis may be accompanied by asthenia. The objective in the administration of the mercurials is to reduce the body weight to a level at which the optimal volume of extracellular fluid remains. This has

* The same may be given by mouth.

been called by Gold and others the "dry weight" When this point is reached the mercurial diuretics usually have little diuretic effect

Untoward effects following the administration of mercurial diuretics are not infrequently encountered Sudden death has been reported following intravenous administration it has not been observed following intramuscular administration The mechanism of death in these patients has not been definitely ascertained It usually occurs quite suddenly immediately following the injection and has been attributed to an allergic factor or a toxic effect of the mercury on the heart The intramuscular route is the most popular method of administration because it is relatively safe has no painful effects and can be administered by a nurse Some care must be exercised in the use of the mercurials in older patients and those with asthenia they should be used with caution in hot weather Such patients may experience weakness apathy leg cramps a shock like state and even death These episodes may be observed as a result of loss of electrolytes especially chlorides and sodium and occasionally calcium Peters has recently observed instances where the plasma sodium was low prior to the administration of the mercurial diuretics Following the use of the mercurial the plasma sodium may drop to a dangerously low level Such untoward effects may be prevented by the administration of smaller doses of the mercurials (for example 0.5 cc) by the administration of salt prior to and immediately following the

poor diet. The estimation of serum electrolytes of patients under prolonged treatment with mercurial diuretics should be a more common practice

Instances of coronary occlusion have at times been observed following the use of the mercurials Whether or not this is the result of increase in the blood viscosity due to excessive dehydration has not been established Occasionally in a previously digitalized patient the mercurial diuretics may be followed by the production of numerous extrasystoles which are believed to be the result of redigitalization due to the action

of this glucoside contained in the reabsorbed extracellular fluid

Even though this drug has been given for long periods of time up to 2 and 3 years and at frequent intervals there is little evidence that it itself produces kidney pathology However occasional instances of renal shutdown with intractable anuria have been observed

Not infrequently patients who have received the mercurial diuretics with good response over a period of months or years reach a period when they no longer respond to this diuretic The treatment of such "mercurial fast" patients involves a rather serious problem One should differentiate such patients from those where oliguria is present due to mechanical factors e.g. in the presence of marked ascites and where the blood pressure has fallen to shock like levels Following the removal of ascitic fluid and restoration of the blood pressure to a more normal level a diuresis may again be observed If without obvious cause, several doses have been given and no diuretic effect is obtained it is usually dangerous to administer the drug further because its retention in the body may be toxic In the

administration of 10 per cent glucose If these methods fail peritoneal lavage has been advised This is a rather dangerous procedure and should be used only as a last resort

Other Diuretics Other diuretics may be used alone or as an adjuvant to therapy with the mercurial diuretics Ammonium chloride 3 to 11 gm per day may be used as adjuvant to the mercurial diuretics but it is usually not necessary The xanthine drugs are occasionally used for their diuretic effect However by themselves they rarely suffice in the treatment of congestive heart failure The following may be given theobromine 0.6 gm three to five times a day theobromine sodium acetate 0.5 gm three times a day theophylline ethylene diamine 0.5 gm three to five times a day Urea in a dose of 20 gm may be administered two to five times a day Because it is difficult to take by itself it is usually given with fruit juices iced fluids or syrup

DIETARY REGIMEN *Salt and Water Intake*
A low calorie, salt poor diet is preferred during the initial stage of heart failure. For this purpose the Karrel diet may be used. This consists of 1000 cc of milk per day which contains 1 gm of salt. The patient is placed on this diet for several days or a week and after a satisfactory diuresis has resulted this may be increased in caloric content and type of food. The fluids may then be increased to 2000 to 3000 cc per day and the salt intake to 1 gm. The importance of a salt poor diet cannot be overemphasized. The normal daily diet contains about 10 gm of salt. Patients with heart failure can eliminate only about 2 to 3 gm per day. The usual salt poor diets in the hospital or at home contain 5 or 6 gm of salt. The salt which cannot be eliminated is retained in the body with the resultant production of edema. The best way to keep a patient on a dietary regimen of about 0.5 to 1 gm of salt per day is to peruse meticulously each item of the diet and make sure that it is salt free. Even salt free bread may be obtained. Salt substitutes may be used to make the diet more palatable. For this purpose Neocurtasal and Cosalt are recommended.

REMOVAL OF EFFUSIONS Removal of pleural effusions and ascitic fluid may indirectly help the heart and may enable the diuretics and digitalis to act more efficiently. Pericardial effusions resulting from congestive failure are rarely large enough to require paracentesis when other methods have failed. Southey tubes may be used in the occasional case where it is necessary to drain off the edematous fluid from the lower extremities.

Digitalis in Heart Failure PREPARATION AND DOSAGE Many preparations of digitalis drugs are available for the treatment of heart failure. The type of preparation depends on individual preference and the mode of administration, whether the drug is given by mouth, intravenously, or intramuscularly. The most popular method of administration is by mouth and the following preparations are commonly used: the powdered leaf, digitoxin, digoxin, digiland, lanatosid C, and cediland. The following table lists the drugs, the amount required for full digitalizing dose, and recommended daily maintenance dose.

TABLE I

Drug	Digitalis Dose Full Digitalization	Daily Maintenance Dose
Digitalis leaf	15 cat units (22½ grains)	½ to 1 cat unit
Dig Land	15 cat units (50 mg)	¼ mg
Digitoxin	12 to 36 mg	0.05 to 0.2 mg
Digoxin	2 to 5 mg	0.25 to 0.75 mg
Lanatosid C	7.5 mg	0.5 to 1.2 mg
Cediland	5 to 10 mg	0.5 to 1.5 mg

The initial digitalizing dose is that recommended for a patient weighing 150 lbs (about 70 kg). However, the dose required for full digitalization in different patients varies considerably, sometimes twice or more of the recommended dose is required. Although the recommended digitalizing dose is sometimes administered at one time, it is best to give half of this dose initially and the remaining 50 per cent in two portions at 12 hour intervals. Toxic effects rarely occur with the lower digitalizing dose mentioned, they not infrequently occur with higher doses. The following patients develop toxic effects on the smaller dose and should be given digitalis with care: patients with aortic stenosis, those manifesting a severe grade of myocardial damage, those with overactive vagal tone and patients in the older age group.

The maintenance dose of the digitalis drugs also varies considerably in different patients and at different times in the same patient. It is suggested that following digitalization the average dose for maintenance be given to the patient. The patient should not be kept on this dose indefinitely but should be frequently checked and the dose increased or decreased depending on the patient's need and response.

Recently the trend has been to administer the pure glucosides, digitoxin, digoxin, cediland, or lanatosid C rather than the powdered leaf. The advantages in doing this are the smaller dosage, the greater accuracy in standardizing the drug and the absence of local irritating effects on the gastro intestinal tract. However, the action of these purified preparations is not always identical with that of the powdered leaf. They vary in the degree of muscular and vagal effects and the dosages even in patients with auricular fibrillation and are difficult to compare with those of the powdered leaf which has been

so extensively used for many years. For example, following the recommended dose of the purified preparation, the ventricular rate in auricular fibrillation may drop to 70 or 80 per minute. When this point is attained, exertion or excitement frequently elevates the rate far above that which would be attained with the patient on the powdered leaf. Additional doses of the purified preparation are required to prevent this excessive response following exercise and emotion. The following point may be made: the minimal dose of digitalis that will decrease the ventricular rate to 70 per minute at rest is not necessarily the optimal digitalizing dose.

In the past few years, digitoxin has largely replaced the powdered leaf for routine digitalization. However, the frequent development of toxic effects in patients under treatment with digitoxin has led to the re-evaluation of the use of this drug in the treatment of heart failure by DeGraff, Batterman and Rose, and others. They found that digitoxin has a greater cumulative effect than other digitalis preparations and that the maintenance dose, 0.2 mg., recommended by Gold, often results in toxicity after about 4 to 5 weeks. It is their opinion that digitoxin offers no advantage over the digitalis leaf and because of the possibility of severe and prolonged toxicity, digitoxin is not the glucoside of choice.

PARENTERAL ADMINISTRATION The intravenous preparations of digitalis drugs and their full digitalizing doses are strophanthin ($\frac{1}{4}$ o gram), digitoxin (12 mg.), cedilanid (16 mg.), and digalen, 3 to 5 cat units. The following preparations may be given intramuscularly: quabain, $\frac{1}{4}$ o gram, or digalen, 3 to 5 cat units.

The intravenous administration of digitalis drugs is indicated in those patients in whom it is mandatory to obtain a rapid effect and where administration by mouth is considered to be too slow and undependable, for example, patients with severe grades of advanced heart failure following the occurrence of rapid auricular fibrillation or flutter. In some of these cases the intravenous administration results in almost immediate and dramatic effects. An effect from strophanthin may be obtained as early as 5 minutes after its administration. It is important to remember that the intravenous route carries with

it added danger of toxicity. This route should not be used in a patient who has been receiving digitalis for the past 2 weeks. It is safer to administer half of the intravenous digitalizing dose and wait one half to 1 hour in order to note the effect of the initial dose before any of the remainder is given. Often a sufficient degree of improvement is obtained with the initial dose to warrant giving additional doses by safer routes (intramuscularly or by mouth). While strophanthin acts rapidly, it has the additional advantage of being dissipated rapidly so that after its full effect is obtained, digitalization by mouth may be started.

The intramuscular route is indicated in those patients where the need for haste is not as urgent as that mentioned above, but where it is desired that absorption be relatively rapid and dependable.

TOLERANCE The tolerance for digitalis varies considerably with the age of the patient, the type and severity of the heart condition, and the absence or presence of heart failure. In general, it may be said that older patients and those with greatly damaged hearts have a decreased tolerance to digitalis and manifest a narrow range between the therapeutic and toxic effects. In such patients, toxic effects may occur long before

damage. Patients with partial A-V block and those with aortic stenosis are apparently more susceptible to the development of increasing degrees of heart block on relatively small doses of the drug.

TOXICITY The most important symptoms of the untoward effects of digitalis are malaise, headache, anorexia, nausea, vomiting, diarrhea, and occasionally psychoses and ocular symptoms. The initial symptoms mentioned, malaise, headache, and anorexia, may be followed by the more serious states

is well to remember that nausea and vomiting may be present as the result of the local irritating effect of this drug on the gastric mucous membrane when the powdered leaf has been given. This is less true when the purified preparations are administered. It

should be emphasized that vomiting is not invariably present with digitalis toxicity, extremely dangerous evidences of its action may be present without either nausea or vomiting. This is especially prone to occur in those with advanced grades of heart disease and in senile patients. Instead, these patients often present marked weakness and asthenia with clear cut evidence of toxicity in the form of dangerous cardiac irregularities. These cardiac manifestations are often more dependable signs of digitalis toxicity than vomiting.

Psychoses are observed as an occasional toxic effect. In those patients where we have observed this to be present, it was apparently the result of the concomitant cerebral circulatory disturbance rather than the direct effect of the drug.

Ocular symptoms in the form of spots before the eyes and various colors (green, blue, and yellow) may be observed. This condition is usually temporary and disappears with the elimination of the drug. The eyegrounds show nothing abnormal. These effects are believed to result from the direct toxic effects of the drug on the primary optic centers in the brain.

There are certain signs which

to
full
the

is indicated when (1) the heart rate drops to 60 or below (2) a formerly regular pulse becomes irregular, (3) a bigeminal pulse is present, (4) the cardiac rate, previously between 80 and 100 suddenly becomes rapid and irregular, 140 to 180 per minute.

Although the clinical evidence of toxicity is important the most accurate method of confirming this suspicion is by means of the electrocardiograph. As initial evidence of its action there is observed depression of the ST segment and inversion of the T wave. Digitalis commonly alters the T wave and ST segment in a definite and characteristic manner. The P R interval, or A V conduction time, becomes prolonged and heart block of various grades may result. In some electrocardiograms several of these evidences of the drug's action may be observed in one tracing. Most of these electrocardiographic alterations may occur within the therapeutic range of digitalis action. The presence of the

following however are unequivocal signs of toxicity: high grade A V heart block, going into complete block, A V dissociation with ventricular escape, numerous ventricular extrasystoles, coupled rhythm, auricular tachycardia with A V heart block and ventricular tachycardia. The treatment of these ectopic rhythms consists of cessation of further digitalis medication. Quinidine may be of help in abolishing the ventricular extrasystoles, coupled rhythm, and ventricular tachycardia.

In summarizing it may be stated that in the administration of digitalis, three points to be noted are (1) the maximal therapeutic effects, (2) the beginning toxic effect, and (3) the definite toxic action. The boundary between the maximal therapeutic and the beginning toxic effect is often not clear cut. It is difficult to determine this point clearly in patients with normal sinus rhythm. The maximal therapeutic effect of its action is most clearly marked in patients with auricular fibrillation. There it may be said to be present when the cardiac rate has fallen to 70 with an elimination of the pulse deficit. This point does not necessarily coincide with the maximal possible degree of improvement in the patient. Edema may still be present and require the use of the mercurial diuretics for its abolition.

Treatment of Acute Left Heart Failure
In general the principles of treatment in acute left heart failure consist of (1) treatment of the cause, namely the underlying heart condition such as coronary artery disease, aortic or mitral valvular disease, or hypertension (2) abolition of certain reflexes and treatment of rapid ectopic rhythm which may precipitate the attack, and (3) decrease of the circulating blood volume so that the damaged heart may be able to perform its functions with a lesser degree of strain.

Dose of morphine sulfate, 10 to 15 mg given alone or accompanied by atropine, $\frac{1}{150}$ to $\frac{1}{15}$ grain. The morphine sulfate may be given subcutaneously, intramuscularly, or at times (during a shock like state) intravenously. The earlier it is given following the inception of an attack, the better will be the therapeutic

result. In many patients administration of this drug alone will suffice to abort the attack in about 10 or 15 minutes. In older individuals, who are sensitive to the effects of morphine, the respirations may drop to 10 or less per minute. In such patients, it is well to administer a respiratory stimulant with the morphine, as for example, caffeine and coramine.

Caffeine with sodium benzoate, 0.5 gm., may be given initially and repeated every 2 to 3 hours for about three doses. This acts as a respiratory and cardiac stimulant. Coramine, 1 cc., may be repeated two or three times over a period of 2 or 3 hours. Aminophylline, 0.3 gm., may be given slowly by the intravenous route repeated in about half an hour. The beneficial effects of this drug depend on its respiratory stimulating effect and possibly its coronary dilator action.

Digitalization may be accomplished rapidly by the administration of strophanthin $\frac{1}{100}$ to $\frac{1}{50}$ grain or 0.8 to 1.6 mg. of cediland intravenously if the patient has not been previously digitalized. If less haste is required, digitalin may be given intramuscularly in a dose of 3 to 5 cat units. Generally digitalization is of less efficacy than the other procedures mentioned for this treatment of the acute attack.

Oxygen may be given by nasal catheter, oxygen mask, tent, and at times under positive pressure. The administration of oxygen is important in left heart failure because the heart suffers five times as much from oxygen lack as does skeletal muscle. The maintenance of a maximal degree of oxygenation is important for the optimal function of the heart, particularly at a time when the pulmonary vascular field available for oxygenation is diminished.

In a plethoric individual, venesection, 250 to 500 cc., is of aid in rapidly reducing the strain on the left heart. This should not be done in an asthenic individual or where the patient experienced frequent attacks of left heart failure, owing to the slowness with which regeneration takes place in such individuals, resulting in anemia. A bloodless venesection may be accomplished by the application of tourniquets to all four extremities. These may be kept on for 10 or 15 minutes, released in one and kept on three extremities at a time. This regimen is of as

much help in reducing the circulating blood volume as a venesection.

The administration of 50 per cent glucose or sucrose has been recommended for the treatment of pulmonary edema, based on their osmotic effects. However, we believe that this is a dangerous method of therapy because, by a shift of fluid from the tissues into the blood, the circulating blood volume is increased, this adds to the strain of the already overstrained heart. We have seen the intravenous injection of these hypertonic solutions precipitate attacks of left heart failure.

Following the attack of left heart failure, the patient should be kept at rest in bed for 1 or 2 days. Frequently he feels quite well the morning following the attack and is able to go about his duties. After an attack of pulmonary edema, these patients frequently develop a mild grade of bronchopneumonia which usually yields to antibiotics and chemotherapy (penicillin and/or combined sulfonamides).

Prophylactic Measures in Patients Subject to Attacks of Left Heart Failure. In patients subject to attacks of left heart failure, the following measures are helpful in preventing recurrent attacks: (1) a period of bed rest may be of aid in resting the heart by keeping the cardiac output at a minimum; (2) restriction of sodium intake to about 0.06 to 0.120 gm. per day and restriction of fluids to about 1200 to 1500 cc. per day; (3) digitalization; (4) diuretics in the form of the mercurials; one injection (2 cc. of mercurhydrin) to be given every week or two, or more frequently, with or without ammonium chloride, 2 or 3 gm. per day; (5) a light supper with little fluid before bedtime; (6) occasionally these patients are helped by sleeping with the head of the bed propped up about 9 inches from the floor; (7) aminophylline, 0.2 gm., t.i.d. by mouth and/or 0.67 gm. administered rectally at bedtime; (8) sedatives preferably the barbiturates; (9) prevention of abdominal distention by careful regulation of the bowels; (10) a dietary regimen to reduce the weight in obese patients.

Surgical Treatment in Heart Failure. Various surgical procedures have been suggested for the treatment of congestive heart failure. These consist essentially of an at

combination of both right and left heart failure. Unfortunately there is as yet no dependable method of treating patients with hypertension so that permanent improvement may be obtained. Treatment by potassium thiocyanate vasodilators and sedatives is only partially efficacious and does not have a permanent beneficial effect on the hypertension. The use of the salt poor diet, the rice diet, and the Smithwick operation is of temporary aid in reducing the blood pressure. In some few cases the Smithwick operation by reducing the blood pressure has been singularly successful in preventing attacks of heart failure.

Other Methods of Therapy IMPAIRED NUTRITION. Poor nutritional states may aggravate and at times precipitate heart failure. Their correction is obtained by an adequate diet, treatment for anemia, vitamins and adequate protein intake by the administration of blood and plasma.

CHEMOTHERAPY AND ANTIBIOTICS. Inflammatory states may also aggravate and at times precipitate heart failure. These may be treated by chemotherapy: penicillin, sulfonamides and aureomycin. Diphtheritic infection should be treated with antitoxin. Unfortunately there is as yet no adequate therapy for active rheumatic carditis. The sulfonamides and penicillin are apparently of benefit as prophylactic measures in cardiac patients.

TREATMENT OF METABOLIC DISORDERS. The adequate treatment of diabetes, particularly the state of coma during the presence of acidosis is of paramount importance since this condition has deleterious effects on the heart. Similar therapy should be directed for other types of altered metabolic states such as hyperthyroidism and hypothyroidism, hyperparathyroidism and hypoparathyroidism, Addison's disease, pheochromocytoma, gout and other metabolic disorders.

ELECTROLYTE CHANGES. Alterations in the electrolyte balance are of great importance in

disease and in various metabolic disorders. The effects of a low serum sodium have already been discussed. Hypocalcemia increases the irritability of the heart muscle. A low serum potassium results in a disturb-

ance of function of the already disturbed heart. We have observed patients with heart failure who manifested little response to the usual methods of therapy, in whom correction of the electrolyte picture resulted in marked improvement.

CLIMATE. Patients who have or are prone to develop congestive heart failure do better in a slightly warm or cool environment. They do not do well in hot weather. The mortality of patients with congestive heart failure is considerable during hot spells. This is probably the result of increase in cardiac output, loss of electrolytes and excessive thirst with difficult elimination of water. The use of air conditioning in hot weather is of considerable benefit to such patients.

SAMUEL BELLET

TABLE III

SAMPLE DIET CONTAINING 2000 CALORIES AND 10 GM SODIUM CHLORIDE

	Food (gm)	Protein (gm)	NaCl (mg)	Calories
Breakfast				
{ Bread	40	3.7	30	104
{ Butter	12	0.1	2	87
{ Jelly	15		5	35
Cream	40	0.9	31	153
Sugar	15			60
Canned apricots	50	0.5	49	37
Cream of wheat	120	1.3	2	44
Egg (boiled)	50	6.6	179	80
Dinner				
{ Bread	40	3.7	30	104
{ Butter	12	0.1	2	87
{ Jelly	15		5	35
Steak (sirloin)	90	19.9	213	105
Rice	20	1.6	13	71
Butter	15	0.2	3	111
{ Fresh string beans	75	1.8	35	32
{ Butter	4			29
{ Apple raw (sauce)	95	0.4	27	60
Sugar	10			40
{ Whipped cream	25	0.6	19	96
Supper				
{ Bread	40	3.7	30	104
{ Butter	12	0.1	2	87
{ Jelly	15		5	35
Roast turkey	60	19.0	203	97
Steamed Irish potato	75	1.5	42	64
Butter	12	0.1	2	87
Lettuce	20	0.2	10	3
Fresh tomato	50	0.5	16	12
Pot cheese	25	5.2		28
Olive oil	5			45
Canned cherries	75	0.8	44	67
	1132	70.5	999	1999

TABLE IV

CARDIAC DIET WEIGHED AND APPROXIMATED*

BREAKFAST			LUNCHES		
	gm			gm	
Milk	100	½ cup	9 AM		
Cream	66	¼ cup	Water	100	½ cup
Cereal (cooked)	100	¾ cup	or crushed ice	100	1 cup
Sucrose	10	3 teaspoons	10 AM		
Glucose	10	6 teaspoons	Orange juice	150	¾ cup
Dextrin maltose	10	0	Lemon juice	5	1 teaspoon
			Sucrose	10	3 teaspoons
			Glucose	20	6 teaspoons
Dinner			3 PM		
Soup { Cream	132	¾ cup	Milk	100	½ cup
Potato	50	½ cup	Cream		¼ cup
Butter	10	2 teaspoons	Flavoring		
Ice Cream	100	¼ cup	Dextrin maltose	12	4 teaspoons
or junket †		¼ cup	Sucrose	5	1 teaspoon
Milk	100	¾ cup			
Water	100	½ cup			
or crushed ice	100	1 cup			
Supper			4 PM		
Soup { Cream	66	¼ cup	Water	100	½ cup
Milk	100	½ cup	or crushed ice	100	1 cup
Sp. nacl ‡	50	¼ cup			
Butter	10	2 teaspoons			
Egg	50	1 egg			
Milk	100	¾ cup			
Custard { Lactose	10	3 teaspoons	7 PM		
Glucose	10	3 teaspoons	Milk	150	¾ cup
			Dextrin maltose	10	3 teaspoons
			or candy		1 st ck

REFERENCES

- Bridges W C, Wheeler H O and White P D. Low Sodium Diet and Free Fluid Intake in Treatment of Congestive Heart Failure. Preliminary Report. *New England J Med* 234:573 1946.
- DeGraff A C and Leliman W A. Acute Toxicity of Mercurial Diuretics. *JAMA* 119:998 1949.
- DeGraff A C and Nadler J E. Review of Toxic Manifestations of Mercurial Diuretics in Man. *JAMA* 119:1006 1942.
- Donovan M A. Cardiac Dyspnea and Its Treatment. *New York State J Med* 45:1756 1945.
- Ellis L B. Medical Progress. Mechanism of Heart Failure and Related States. *New England J Med* 298:384 311 1943.
- Ellis L B. Relative Importance of Sodium and Fluid in Management of Congestive Heart Failure. *New England Heart A* p 33 1942.
- Fishberg A M. *Heart Failure*. Philadelphia: Lea & Febiger 1940.
- Fox T T, Gold H and Leon J. Hypersensitive to a Mercurial Diuretic with Observations on Its Mechanism. *JAMA* 119:1497 1942.
- Fletcher P H and Schroeder H A. Studies on Congestive Heart Failure. Impaired Renal Excretion of Sodium Chloride. *Am J Med Sci* 204:50 1942.
- Gold H et al. Studies on Purified Dog's Glycosides. Single Dose Method of Dog's Glycosides. *JAMA* 119:998 1942.
- Gold H et al. System for Routine Treatment of Failing Heart. *Am J Med* 3:665 1947.
- Grollman A et al. Sodium Restriction in Diet for Hypertension. *JAMA* 129:533 1945.
- Harrison T R. *Failure of the Circulation*. Baltimore: Williams & Wilkins Company 1939.
- Karel P. De la cure de l'asthme. *Arch gen de med* 8:513 1866.
- Kempner W. Compensation of Renal Metabolic Dysfunction. Treatment of Kidney Disease and

- Hypertensive Vascular Disease with Rice Diet
North Carol na M J 6 61 1945
- North W Gold H and Clarke D A Quantitative Observations in Mercuhydrin and Mercuripurin
J Pharmacol & Exper Therap 84 284 1945
- Newburgh L H Foundations of Diet Therapy
JAMA 105 1034 1935
- Poll D and Stern J E Untoward Effects of Diuresis with Special Reference to Mercurial Diuretics
Arch Int Med 58 1087 1936
- Schemm F R High Fluid Intake in Management of Edema Especially Cardiac Edema Details and Basis of Regime
Ann Int Med 17 952 1942
- Volm I F Levitt M O and Martin R Studies on Mercurial Diuresis Sudden Death Following Intravenous Injection Report of 3 Cases with Electrocardiographic Studies in 2
JAMA 129 12 1945
- Wa-
r
t
P
C
u
- Weiss S and Robb G P Cardiac Asthma (Paroxysmal Cardiac Dyspnea) and Syndrome of Left Ventricular Failure
JAMA 100 1841 1933
- Wishart J H and Chapman C B Decumaryl Therapy in Congestive Heart Failure
New England J Med 239 701 1948

DISEASES OF THE BLOOD VESSELS

HYPERTENSIVE VASCULAR DISEASE

General Considerations as Related to Treatment Treatment of patients with hypertensive vascular disease is based on a definitive diagnosis and classification of the kind of malady from which the patient suffers. Arterial hypertension like fever or leukocytosis is of multiple origin. No discussion of its treatment is possible which does not presuppose an estimate of the nature, extent and rate of progress of the disease.

The term "hypertensive vascular disease" has value because it is broad and inclusive. It means a state in which arterial tension is increased over long periods of time and one which is usually associated with premature damage to blood vessels and to the tissues and organs they supply. It has no etiologic and often little physiologic connotation. It includes a most common lethal disease of adult life, namely essential hypertension. The cause of this disease is unknown. The term also includes a variety of secondary, sometimes transitory, hypertensive states the origin and nature of which are either known or suspected on adequate clinical and functional grounds. While this review of treatment is concerned more particularly with "essential hypertension" it is also necessary to review some of the other types of hypertensive disease which simulate essential hypertension.

Essential hypertension is characterized by persistent elevation of systolic and diastolic arterial pressures. In its early stages which

begin probably in the 20s and 30s or in adolescence the elevations of arterial pressure are transitory and subside promptly on rest and minor reorientation of habit and attitude. In its later stages the elevations of arterial pressure are more severe, more lasting, more resistant to minor modes of treatment. Finally the levels of pressure even at bed rest and under sedation tend to stabilize at high levels. At any stage in the disease but as might be expected more commonly during the phases of persistent and severe elevation of pressure there appear evidences of advancing arteriolar sclerosis which are reflected in damage to the brain and in lesser degree to the retina, kidney and other vascular beds. With this go signs of damage to the function of the myocardium. In a small percentage of patients essential hypertension is manifest as the syndrome of malignant hypertension in which the progress of vascular damage is catastrophically accelerated with predominance of damage in the renal vascular bed. The same syndrome of accelerated arteriolar damage may be precipitated by other hypertensive disease states.

The so called "secondary" hypertension is the hypertensive states of known or suspected origin. It can be classified according to their causes as (1) neurogenic, (2) endocrine, (3) vascular and (4) renal. As examples we note the hypertension in chronic porphyria as of presumptive neurogenic origin, the hypertension and nephrosclerosis of Cushing's syndrome, adrenal cortical

tumor and adrenal medullary pheochromocytoma as of endocrine origin the hypertension of coarctation of the aorta as a type of cardiovascular hypertension and that of

and diagnosis lies in the fact that for example cases of pheochromocytoma and some with unilateral renal disease can be cured by surgical removal of the offending organ. The hypertension of aortic arteriosclerosis is of particular significance in considering the treatment in hypertensive vascular disease. The increase in arterial pressure is largely if not entirely systolic. It is due to a failure of the aorta which has become inelastic to expand and adapt its capacity to the blood ejected from the heart during its beat. There is consequently an abrupt rise in systolic tension in the large arteries as this blood is forced into them on its way to the arterioles. The extent to which systolic pressure rises depends on cardiac rate and cardiac output and in the last analysis most of all on stroke volume. Consequently anything which tends to change stroke volume or cardiac output tends to have a parallel effect on systolic tension. Thus it is not paradoxical but entirely logical that this form of hypertension in which the large arteries are least elastic is also the form in which the levels of systolic tension fluctuate most widely. Cardiac output in intact human beings is predominantly under nervous control but varies also with metabolic rate, tissue demands and other factors. Therefore it is a common experience that mild measures such as rest, reassurance and sedation and control of obesity which tend to decrease cardiac output often have dramatic results in decreasing arterial tension in elderly people. It is this responsiveness of pressure levels in arteriosclerotic hypertension which has led so many unwary clinicians into unwarranted therapeutic claims. Similar

sion occur which as time goes on become persistent at least during casual measurements. The diastolic pressure is little if at all increased. The underlying disease is a generalized arteriosclerosis. There are to be found therefore evidences of arteriosclerosis in the heart, brain and kidneys. But this disease has a slow rate of progress. Consequently although vascular accidents can occur without warning most of these people live to nearly a normal expectancy of life.

The treatment of this condition is basically the treatment of old age and of vascular complications as they appear. Many of the

Essential Hypertension Just as the first step toward treatment in arterial hyperten

tension has been made its treatment again depends on further subclassification. This subclassification is made from the state and kind of disease and its rate of progress.

First of all there is the "prehypertensive" the youth with transitory elevation of arterial tension and usually other signs of vasomotor instability. Essential hypertension has appeared often among his ancestors. In the present state of knowledge it seems likely that many of these will sooner or later develop the disease in an established form. The problem is to make its appearance come later rather than sooner. Perhaps the best that can be done is to aid these people in orientation in life situations which will not place excessive demands on them and to counsel them toward the adoption of a serene and stable point of view.

Next is the patient whose hypertension is persistent over long periods who shows minimal evidences of advancing vascular disease in the heart, brain, eyes or kidneys and who believes himself to be in good health. Among these is a group whose pattern is one of emotional instability of anxiety and of central nervous disequilibrium. This form of essential hypertension is called provisionally "neurogenic." One group of these patients constitutes the "hypertensive diencephalic syndrome" described by one of us. This condition is

the only transient increases of systolic ten

characterized by episodic discharges of emotional energy, evidenced by elevations of arterial pressure, weeping, blushing, of a macular spotty type, on the upper chest and neck, sweating, gastro intestinal activity, and other signs of autonomic release, including

tachycardia, "nervousness," sweating and frequently elevated basal metabolic rates (to levels of about + 20 to + 30) many of these patients are subjected to thyroidectomy, or receive antithyroid drugs, and, of course, without benefit. A point in differential diagnosis is the level of the plasma cholesterol which, in these patients, is not decreased as it would be in hyperthyroidism. Still another group of patients with early hypertension of seeming 'neurogenic' origin are people who by racial and social constitution are emotionally labile and active, and whose resistance to pain or distress is low.

The symptomatology of patients with hypertension of apparent neurogenic origin is varied and often dramatic. Fortunately, the rate of progress of arteriolar and cardiac damage in patients of this sort is usually slow, possibly because the blood pressure is not persistently elevated. These patients more than others tend to do well on general therapeutic measures, and many respond poorly to more drastic procedures, such as sympathectomy.

Next there is the large group of patients whose disease is almost free of symptoms until perhaps some complication such as congestive cardiac failure or apoplexy or the onset of nocturia or hematuria draws them to the physician's office. The problem of evaluating the nature and degree of vascular disability and the rate of its progress is especially urgent in these, since signs of progressive damage will tend to change the orientation of treatment. This evaluation consists of a thorough examination which includes inspection of the retina and retinal vessels, measurement of heart size, an electrocardiogram, and measurement of maximal urinary concentrating power by the Addis test. With these data to form the base line, the physician can estimate the rate of progress, or rejoice in the stabilization or recession of the disease at later examinations.

Finally there are the patients noted above who show the syndrome of malignant hypertension, characterized by destructive arterial and arteriolar changes with retinal hemorrhages and papilledema, weight loss, hypertensive encephalopathy, cardiac failure, and progressive renal damage with hematuria and proteinuria. In these, decision as to treatment must be made instantly and before vascular damage has become irreparable.

General Measures Both patient and physician tend too much to neglect measures of treatment of hypertensive disease which are general and most of which fall under the definition of the basic hygiene of life. The neglect is perhaps due to a wish that there would be some specific which will take care of everything which there is not. Fortunately, however, general measures have great value in slowing the rate of progress of essential hypertension in all but its most severe form.

A prime point is the decision of the patient to come to terms with his disability, that he recognizes that, in order to prevent invalidism he must channel his activities with due regard to his condition. This channeling is in the direction of moderation in work, and in play, and, if there is to be success, let it be only in rest and recreation. The basic aim is to secure a serenity and equanimity of mood, purpose, and action which will protect the patient from undue stress of mind or body.

His work should be limited well within the borders of fatigue. It should in most cases be noncompetitive. It is a difficult decision for men and women who feel themselves in the best of health and productivity to lay aside some of their ambition for power and responsibility in order to protect themselves and their home, but it is often a necessary one. We do not suggest that the patient should retire from his work and shut himself up making baskets—which would almost certainly make his condition much worse. We mean simply that he should, as far as pos-

technics and skills.

Most patients will approach the problem of a rerouted existence in better spirit if they

can be brought to understand something of the nature of their disease. There are vast stores of misinformation on the topic available from both quack and lay circles. The physician who refuses counsel and inquiry exposes his patient to the menace of these, without any gain for himself. It is usually much better to encourage the patient to ask questions and to answer them fairly and honestly. The physician may be aided in this educational program by prescribing for the patient a manual on hypertension intended for lay use. Perhaps the only exception to the free and full provision of information is the answer to the question "And how is my pressure today?" This question is perhaps the best lead into a general discussion of the nature of the disease, of the variability of arterial pressure, and of the impossibility of measuring progress from single determinations. And from such a discussion may come still more understanding and co-operation.

The specific problem of dietotherapy is dealt with below. As far as diet enters into the general measures of control of hypertension, it is merely by the patient's extending to this aspect of life, as to every other, his general program of moderation. He should eat less, especially when he is overweight. He should perhaps be told that a 1 per cent

tea, tobacco, and alcohol, and of sexual intercourse.

The program of recreation is dependent on the individual's interest. He should at least forego violent physical exertion and extremes of competition, seeking constructive and satisfying diversion without any particular achievement.

Specific Measures: POTASSIUM THIOCYANATE. This salt has three actions that are use-

ful: (1) It relieves headache. The latter is its most useful action. The blood level should not be allowed to exceed 12 mg per cent and the usual therapeutic range averages 8 to 12 mg per cent. Often as good results are achieved with somewhat lower levels. The dose is that required to achieve this level. Enteric coated pills should be avoided and the thiocyanate

blood level should be determined in a competent laboratory rather than by short cut methods which often yield highly inaccurate results.

If toxic manifestations occur, such as maculopapular rashes, confusional states, or goiter, the drug should be immediately discontinued.

EXCESSIVELY LOW SODIUM DIETS. The use of low sodium diets has recently been revived, but now the restriction is even more severe, not more than 200 mg of sodium being allowed daily. This level is extremely difficult to attain in most patients and is altogether impractical for some.

The results in our patients have been only moderately encouraging. At least 10 to 15 per cent show a significant fall in arterial pressure and some feel better. Administration of salt to these patients is associated with a rise in blood pressure. It appears that there is some direct association between the change in salt content of the diet and the height of the arterial pressure in these particular patients.

Occasionally, circulatory collapse occurs from the severe salt deprivation, hence the treatment has potential dangers. These can be exaggerated because most patients when not in the hospital under rigorous supervision do not keep their salt intake below 0.5 gm.

Those of us who remember the era when low salt diets were being indiscriminately prescribed for hypertension recall that at times some lowering of pressure occurred apparently as a consequence of the low salt intake. But at that time, the intake almost never fell below 1 gm of sodium chloride. It thus remains to be determined whether the drastic restriction now suggested is really necessary. At best relatively few patients will be benefited from drastic salt restriction, but for these, it may well be worth the effort.

The use of amberlite resins has been suggested as a shortcut to a salt-poor diet. It is much too early to recommend their general use. Potentially, they may do serious damage by removing other important constituents from the gastrointestinal tract.

RICE DIET. The Kempner rice diet and

protein content, which in the Kempner regime is less than 20 gm and in the assumption that other foods contain unidentified toxic substances not present in rice, which embarrass the kidneys. Two hundred and fifty to 350 gm of rice (dry weight) are taken daily. All fruits are allowed except nuts, dates, avocados, dried or canned fruit, or fruit derivatives to which substances other than white sugar have been added. Not more than one banana may be taken a day. White sugar and dextrose are allowed ad libitum. On the average, a patient takes about 100 gm daily, but if necessary, as much as 500 gm may be used. Tomato and vegetable juices are not allowed. Usually no water is given and the fluid intake is limited to 700 to 1000 cc of fruit juice per day. Supplementary vitamins are added—vitamin A, 5000, D, 1000 units, thiamin chloride 5 mg, riboflavin 5 mg, niacinamide, 25 mg, calcium pantothenate, 2 mg. Some form of iron is desirable. Rest in bed is neither necessary nor desirable. Weight may decrease markedly during the first 20 days.

The diet should be continued without modification according to Kempner, until those conditions which were the indication for its use have disappeared. Then small amounts of nonleguminous vegetables, potatoes, lean meat or fish (prepared without salt or fat) may be added.

Nitrogen equilibrium is said by Kempner to be maintained in spite of the 20 gm protein content of the diet. This has been denied by others (Schwartz and Merlis). Blood non-protein nitrogen is lower than in normal or fasting human beings, i.e., 27 as compared with 34 mg per 100 cc and urea nitrogen 141 mg before the diet and 78 mg after. Hypercholesterolemia decreases markedly with the rice diet. Two hundred of 284 patients with hypertensive vascular disease (70 per cent) had cholesterol concentrations of at least 220 mg per 100 cc, 132 exhibited a decrease to normal levels. Free cholesterol and cholesterol esters decrease on the rice diet in about the same proportion. There was a decrease of 99 per cent of the sodium in the urine, a 43 per cent decrease in serum sodium, and an insignificant increase in potassium concentration.

The amount of protein given is less than the minimum for maintaining equilibrium

estimated by several other investigators. In deed, actual measurement of nitrogen balance on the rice diet by Schwartz and Merlis showed it to be negative over several months. But one of their subjects, whose hypertension seems to have been severe, was also much improved by it. Still, there is no conclusive evidence that severe restriction of animal protein is of real value in hypertension except as it becomes necessary with the advent of renal failure.

Kempner's indications for use of the rice diet consist of all serious instances of acute and chronic glomerulonephritis, heart failure which does not respond to the customary salt restriction and drugs, arteriosclerotic and hypertensive vascular disease with cardiac, cerebral, retinal, or renal involvement, uncomplicated hypertensive vascular disease when a more liberal regime, weight adjustment, restriction of activities, sedatives etc have failed. It is suggested the diet be tried before sympathectomy is considered.

Our own experience with the rice diet has been limited to some 50 patients. Some of them would not stay on the diet because of its monotony. Among those who did so after a prolonged control period, effects on the blood pressure have not been so impressive as when the diet was started shortly after coming under our care. A fall in renal blood flow in some has occurred which so far has seemed reversible. The eyegrounds of one patient may have cleared as the result of the diet, but this is uncertain for a variety of reasons. Thus, it is our view that the rice diet deserves much more careful study.

The divergent conclusions reached by different investigators lead only to the conclusions (1) that the problem is still in the investigational phase, and (2) that the investigations should be performed seriously and with every possible safeguard. One of the essential safeguards least employed is an

physician contact. Casual blood pressure readings over even many years, however constant they may be, do not replace as controls frequent measurements before and during the periods of dietary control. Another factor in prescribing the diet is the patient's en-

thusiasm for it. Often he can only be persuaded to it by promises of relief or threats of serious complications which few physicians can conscientiously subscribe to. Still, some encouragement may be necessary, for it is only the rare patient who will take a detached and scientific view of a rigid dietary scheme.

The effects of weight loss due to the diet have not been adequately evaluated. European experience during the war, as well as common clinical observation, suggest that these play a much more important part in determining the decrease in arterial pressure than deprivation of animal protein and provision of protein of vegetable origin.

SYMPATHECTOMY Three types of sympathectomy are now being practiced, the dorsolumbar operation of Smithwick, the *splanchnic nerve resection* and ganglionectomy of Peet, and the "total" sympathectomy of Grimson. The Smithwick operation currently has the greatest popularity.

While there has been much work on the nature of the changes produced by these operations, the problem has received no satisfactory solution. As matters stand, it can only be said that in some patients the operations lower blood pressure along with both subjective and objective evidence of clinical improvement. Unfortunately, it must be added that of the many tests proposed for patient selection, none have proved serviceable. We are left then with no alternative but to make an arbitrary choice of candidates according to experience.

Our selection is largely limited to two groups of patients: those with rapidly advancing vascular disease, and those with early or even moderately advanced malignant hypertension. We do not feel justified in operating on young people with essential hypertension in whom the rate of progress of the disease is not known. Within this rather arbitrary framework we expect about 10 to 15 per cent among the essential hypertensives to show marked improvement, 30 per cent to show moderate improvement, 40 per cent to show subjective improvement, and the remainder to be without benefit. Indeed, in a few patients almost complete remission has occurred, lasting for periods up to 3 years, seldom more.

It should never be forgotten that there is

some danger connected with the performance of the operation, and therefore it cannot be recommended lightly.

The fact now seems to be established that when a marked fall in arterial pressure occurs as the result of operation, objective betterment in the electrocardiographic pattern, size of the heart, and appearance of the vessels in the eyegrounds usually follows. There is no evidence that the denervation of the kidneys causes any direct increase in their excretory efficiency though with improvement in the general conditions of the blood vessels some increase in urinary output may be noted.

KIDNEY EXTRACTS The reasons for the search for substances in the kidneys which might lower blood pressure need not concern us here. Extracts of kidneys have been prepared which lower blood pressure and cause improvement in the clinical condition of patients. But the mechanism by which these extracts act is entirely unknown.

Three possibilities currently present themselves: (1) the pyrogenic and so called "non-specific" effects associated with the injection of foreign proteins, (2) the presence of a substance inhibitory to the contraction of blood vessels, (3) the production of antirenin, (4) the presence of angiotonases.

do not achieve the same result as the active renal extracts. The presence of inhibitory substances is demonstrated by the inhibition of adrenalin and angiotonin when kidney extract is injected intravenously into anesthe-

renin, it is possible, though as yet undetermined, that this may be part of the action. Although kidney extracts contain angiotonases, they are probably not concerned in their activity since we found 8 years ago that extracts rich in them were not active in patients.

It is the belief of a few investigators that certain types of extracts of kidneys have these beneficial effects, but none to date has been able to prepare an altogether suitable extract. Such a search is naturally a tedious and expensive job, since patients must be the

test objects and nothing is known of the chemical nature of the substance sought

There is some evidence which suggests but does not prove some degree of specificity. Kidney extract will reverse the intrarenal hemodynamic change usual in many cases of hypertension to a more normal one. Further, cardiac output will be elevated in hypertensive patients when the mean pressure falls.

It is quite clear that work along this line prematurely

VITAMIN A As the result of the clinical report of Villaverda and Pena, large amounts of vitamin A have been administered to hypertensives in this country. But our results have shown clearly that vitamin A of itself, even in great amounts, does not lower arterial pressure, although it sometimes improves renal function. In hypertensive animals, some samples of fish body or liver oils seem to lower arterial pressure. The investigation of this phase of the problem has not progressed sufficiently far to justify an opinion as to its value.

RUTIN In 1860 rutin was isolated from buckwheat but it was not until recently that it has received clinical trial. The latter was

Reports on the value of rutin are highly contradictory. In no small measure this is due to the wide variability of the results of the various tests of capillary fragility. In deed, at present it seems fair to indicate that none of the tests have been studied sufficiently carefully nor has the consistency of the results been demonstrated. Little or nothing is known of the natural history of increased capillary fragility.

Several authors have believed rutin prevents or cures the hemorrhages in diabetic retinitis, and if it had the desired effect on the capillaries and if hemorrhages result from increased fragility, this would appear to offer opportunity for successful treatment

The more recent and careful articles find rutin of no value in the treatment of diabetic retinitis.

Some time ago, rutin was suggested as a

treatment of a group of hypertensives in whom he believed he had demonstrated increased capillary fragility. The fragility in many cases became normal. It is not clear what, if any, effect this had on the course of the disease.

Next, rutin was used in the hope that cerebral hemorrhage might be avoided on the theory that hemorrhage is due to capillary bleeding. There seems to be no cogent evidence that this is so. Since it is impossible with present methods to know when cerebral hemorrhage is going to occur, the problem of studying the prevention becomes one of the greatest difficulty. At present there is no reason whatever for prescribing this drug for the prevention of cerebral hemorrhage despite drug house literature urging such indiscriminate use.

The most significant evidence that rutin has some pharmacologic action comes from its use in experimental animals in preventing or reducing the hemorrhagic lesions induced in dogs by single large doses of roentgen rays. It may also be of some value in purpura hemorrhagica. Despite the claim that it conferred protection in anaphylactic and histamine shock, this has not been substantiated by recent work.

Clearly the widespread sale of this material on the basis of published evidence was most unwise. The drug houses have presented only the side of the picture which makes the drug saleable, rather than that showing it to be of only minor or of no value in treatment of hypertension. Unless better evidence is forthcoming rutin has no place in the management of the hypertensive patient.

BACTERIAL PYROGENS IN THE TREATMENT OF MALIGNANT HYPERTENSION Daily administration of concentrated bacterial pyrogens, especially those from *B. prodigiosus*, over periods of weeks to months, often causes remarkable clearing of the pathologic changes in the eyegrounds of malignant hypertension. Thus in a series of patients studied by

Taylor, Corcoran, Fertig and Page,* average arterial pressure (systolic and diastolic) was reduced from a mean of 126 to 100 mm Hg. Papilledema disappeared in all but 2 and fresh exudates disappeared. Improvement was also noted in the electrocardiogram and the heart size diminished.

Except for the persistent elevation of arterial pressure, remissions have lasted for an average of 2 years. Of the remaining 19 patients, 11 responded more briefly, while 8 showed no change. All but 2 of these are dead and these 2 are presently under treatment.

The greatest drawback in the treatment is that tolerance to the pyrogen usually appears in from 5 to 19 weeks, after which arterial pressure usually rose to the control levels but without reappearance of the malignant syndrome.

It has not been possible to select those patients who will respond to pyrogen therapy. Six patients who were virtually blind and 4 who had congestive failure responded favorably. In general it appears that if renal excretory function is reduced by 50 per cent or more the response will be poor, or at least no more than temporary.

This treatment must be regarded as experimental until more experience has been gained. In view of the gravity of the disease the results so far obtained justify its further use when the patient can be under the daily care of the physician.

IRVINE H. PAGE
A. C. CORCORAN

REFERENCES

Ayman, D. Arterial Hypertension in Oxford Med.

Hypertensive Disease. New York: The Commonwealth Fund, 1944.

* These authors have recently advocated the use of pyrogen (Baxter Laboratories) when the pyrogen treatment is to be used. This is given in a single intravenous injection, the first dose being 0.5 cc.

Page, I. H. *Hypertension, A Manual for Patients with High Blood Pressure*. Springfield, Ill.: C. C. Thomas, 1943.

Page, I. H. and Corcoran, A. C. *Arterial Hypertension: Its Diagnosis and Treatment*. Chicago: Year Book Publishers, 1945.

Page, I. H., and Taylor, R. D. Pyrogens in the Treatment of Malignant Hypertension. *Mod. Concepts Cardiovas. Dis.*, 18: 51, 1949.

DISSECTING ANEURYSM OF THE AORTA

Various statistical studies suggest that about 90 per cent of patients die in the initial attack, although with continued and careful study and earlier recognition of the syndrome this almost hopeless outlook has changed considerably and it is likely that about 20 per cent now survive. Many patients have lived for long periods after rupture. Pathologists are acquainted with patients who show the so-called double aorta due to a previously ruptured dissecting aneurysm with complete endothelialization of the new channel and adequate function.

The author is impressed with the similarity of the picture of acute dissection of the aorta with rupture to that of extensive myocardial infarction from thrombosis or from the less frequent and less accepted coronary spasm. The former early hopelessness in the management of acute coronary thrombosis has given way to a high measure of promise in the efficacy of studied therapy. The same effort should now be trained on the syndrome of ruptured aneurysm which is increasing in frequency with the known higher occurrence of hypertension. A co-operative approach by internist, roentgenologist, electrocardiologist and qualified vascular surgeon will bring about a more dependable

farcion. It has many or all of the features of complete or incomplete obstruction to the ingress of oxygenated blood to the heart, lung, intercostal vessels, brain, abdominal viscera, upper or lower limbs. The first consideration is to relieve the agonizing pain and secure rest for the patient. This may be accomplished by full doses of morphine or pantapone or similar preparations. In patients known to be sensitive to morphine, pantapone

would seem preferable. It may be necessary to give morphine in a dosage of $\frac{1}{2}$ to 1 gram (30 to 60 mg) and pantapone in a dosage of $\frac{1}{2}$ to 1 gram (40 to 60 mg), and such medication should be continued at regular intervals in an attempt to obtain complete physiologic rest. Both may be combined with full dosage of atropine. Vomiting calls for a substitution at once of narcotics known to be

ture is followed by a rather classical picture of acute aortic insufficiency with consequent final pulmonary engorgement and right heart dilatation. Oxygen in full concentration is indicated. This may best be accomplished by placing the patient in an oxygen tent although if, as is seen occasionally, the patient is distressed by the emotional tension of be-

tial bed rest. The patient should be protected by adequate and competent nursing so that all exertion is kept at a minimum. Nursing care must extend around the clock if the patient is to receive the maximal protection from extension of the process. The period of rest should be comparable to that advised in patients with severe myocardial infarction. Absolute rest should continue for at least 6 to 8 weeks, much restricted effort for another 6 to 8 weeks, and gradual resumption of activity over another period of 6 to 8 months. It is of course recognized that such limits are clearly arbitrary but not prohibitive if we are to increase the percentage of cured cases.

Undoubtedly a high degree of angiospasm is present in the major vessel of the arterial tree when dissection is initiated. The process is well understood in smaller vessels of the arterial tree and the same process must exist in this major vessel. Angiospasm explains in part the tumultuous picture of early aortic tearing seen in the overwhelming pain, suffocation and shock. For this reason it is reasonable to suggest that adequate intravenous doses of papaverine be given slowly. This medication can be given in the dosage of $\frac{1}{2}$ to 1 gram (30 to 60 mg) repeated as indicated by the failure to relieve pain, evidence of advancing ischemia, and the persistence of sweating, pallor, shock, and similar symptoms.

The author can see no dependable reason for giving anticoagulants in this condition. Our hope is to provoke thrombosis rather than increased fluidity, at least so far as the major vessel is concerned. Whether vitamin K, vitamin C, or thromboplastic drugs can or will accomplish a measure of help is problematical.

In a considerable number of patients, rup-

cure may be of service in supporting an otherwise acutely overdilated though in sufficiently filled arterial system.

In the presence of cardiac decompensation adequate doses of digitalis are indicated but we doubt the value of quinidine.

For the first few days following rupture a liquid easily absorbed diet is necessary. The introduction of large amounts of fluids into the vascular system is contraindicated. A sensible balance between fluid intake by mouth and by the intravenous route is in order. Plasma and blood transfusions have been suggested by many, but here again it is unlikely that either plasma or whole blood is the answer to the problem.

Part of the difficulty incident to rupture of a dissecting aneurysm comes not from the dissection alone but from the compromise of the main aortic lumen by the pressure of a column of blood behind the intima, not unlike the subintimal and medial hematomas described by Wartman in coronary thrombosis. The relief of this blockade by the reestablishment of an ostium into the main channel is worthy of more than passing interest. Congenital heart disease was long regarded as beyond surgical attack while today it is almost commonplace. Since the introduction of antibiotics and the rapid advances in the technique of anesthesia, surgical attack on the heart and its blood vessels gives promise of an extension to this type of treatment for dissecting aneurysms. Two complications of rupture of dissecting aneurysm merit surgical thought. In various studies one third to one half of the cases had perforation into the pericardial sac with death due to hemopericardium, cardiac tamponade and acute compressive myocardial failure. Early aspiration of the widening peri-

cardial area with vigorous surgical attack may some day yield results of real value. It is also known that in 20 to 30 per cent of these cases of rupture of a dissecting aneurysm perforation occurs into the pleural cavity with resultant rapidly increasing compression of the lung by hemothorax. Here mere aspiration of fluid blood will accomplish nothing and more radical and dramatic effects might be produced by blockade of the bleeding area with coagulants. It is certain that more vigorous surgical attack should be referred to the aneurysms which dissect into the abdominal vessels and occlude the vessels to the limbs and other structures since here undoubtedly part of the difficulty is again a mechanical blockade of the main lumen.

Most of the recorded cases of ruptured dissecting aneurysm of the aorta occurred in patients who have had manifest hypertension. Adequate treatment of the hypertension may prevent the development of a dissecting aneurysm and its subsequent rupture. Certainly any patients with chronic hypertension marked sclerosis and widening of the arch of the aorta who have given any suggestion of dissecting aneurysm should be cautioned against overexertion both physical and emotional. Bronchoscopy is clearly contraindicated in the presence of a suspected ruptured aneurysm.

LEROY H. SLOAN

ORTHOSTATIC (POSTURAL) HYPOTENSION

The typical syndrome of orthostatic hypotension is characterized by a marked fall of blood pressure and usually a relative bradycardia in the upright position, impairment of sweating, impotence and accentuation of symptoms in hot weather. The condition is frequently associated with certain diseases of the central nervous system but may occur independently of any recognizable central nervous system disease. In the latter or primary type of orthostatic hypotension the site of the primary defect is thought to be in the hypothalamus although this has not been definitely established.

Although the pathogenesis of this syndrome is by no means entirely clear, defects in the control of reflex sympathetic vaso-motor function and cardiac rate in the up-

right position have been considered generally to be the most important factors. Some observers feel that the fault lies in failure to maintain adequate venous return to the heart in the erect posture as the result of pooling of blood in the lower extremities (MacLean and Allen, MacLean et al.). Although this concept has not been generally accepted, evidence would seem to indicate that such pooling of blood is a contributory factor in the symptom complex. A decrease of blood volume and hemoconcentration has been demonstrated in the upright position and it has been suggested that abnormal filtration rates aggravate the circulatory disturbance (Hallock and Evans).

The treatment of orthostatic hypotension is not satisfactory and at best is only palliative. When present any associated disease of the central nervous system should receive appropriate treatment. These patients must keep their activities at a minimum during hot weather and avoid standing still for long periods.

Various mechanical procedures such as the use of tight abdominal and leg binders, sleeping in the "head up" position and shifting the feet and shuffling movements while standing seem to lessen the tendency to decrease the blood pressure and may even suffice in an occasional case with mild symptoms. Some patients object strenuously to the use of binders especially in warm weather.

The use of the various vasoconstrictor drugs has been reported to be of benefit in some cases. Ephedrine sulfate or neosynephrin hydrochloride may be administered several times daily in $\frac{1}{4}$ grain (20 mg.) dosage. If amphetamine sulfate is used it is best to give $\frac{1}{4}$ to $\frac{1}{2}$ gram (5 to 10 mg.) every 3 to 4 hours. Combinations of these drugs may be used at the same time. We have not been impressed with the value of these drugs in the treatment of orthostatic hypotension since their effects are transient at best and usually disappear over a period of time. The same appears to be true of epinephrine hydrochloride either in aqueous or in oil solution.

Brilliant results with the use of desoxy corticosterone acetate and sodium chloride have been reported. If desoxycorticosterone acetate is used it should be administered

weight gain. The administration of 2 to 5 gm of salt daily is usually adequate. Although our experience with the use of desoxycorticosterone acetate in the treatment of orthostatic hypotension has been limited to a few cases, the results have been sufficiently encouraging to warrant further trial of this form of therapy. However, the potential dangers are considerable, especially when the drug is employed in conjunction

from the administration of sodium chloride alone.

There is no satisfactory specific remedy for the anhidrosis. Pilocarpine will produce sweating in the anhidrotic regions but its use is not practical. Improvement of the reaction of the blood pressure to standing may be accompanied by return of sweating and sexual activity.

RICHARD M. SHICK
WALTER F. KVALE

PERIARTERITIS NODOSA

(Polyarteritis, Panarteritis, Necrotizing Arteritis, Kussmaul-Maier Disease)

Periarteritis nodosa is an inflammatory disease of the arterial system which involves chiefly medium sized and small arteries and arterioles. The terms "polyarteritis" and "panarteritis" are considered to be more descriptive of this rather uncommon condition, for actually the disease process involves all coats of the artery and nodular lesions may be entirely absent.

Although periarteritis nodosa generally is considered a fatal disease, spontaneous remissions and apparent cures may occur. The course may be acute, subacute, or chronic and it may last from a few days to several years. It is important therefore to exercise due caution in evaluating the results of any therapeutic measures in this condition.

Actually there is no known definitive therapy which either prevents, or affects the course of, the disease. Symptomatic treatment is all that can be offered. It generally consists of measures directed toward the

organ or set of organs involved in the disease process. This must of necessity be extremely varied and is usually unsatisfactory.

It has been reported that derivatives of sulfanilamide have effected a cure in some cases but in our experience neither the sulfonamides nor penicillin has been of any apparent value. We have had no experience with streptomycin or the newer antibiotics aureomycin and chloromycetin, in the treatment of this disease, but we have no reason to believe that they would be of value.

The possibility that some cases of periarteritis nodosa may be due to hypersensitivity has suggested the use of the antihistaminic drugs. Although our results with the use of these drugs in a small group of cases have not been impressive, we feel that this type of treatment warrants further trial.

The recent reports of the effects of the adrenal cortical hormone, 17 hydroxy-11-dehydrocorticosterone (cortisone) and of pituitary adrenocorticotrophic hormone (ACTH) on rheumatoid arthritis and acute rheumatic fever are encouraging (Hench et al.). It has been suggested that these compounds may be useful in the treatment of other so-called diffuse collagen diseases, including periarteritis nodosa. It is hoped that a more adequate supply of these preparations will be available for use in these conditions in the near future.

RICHARD M. SHICK
WALTER F. KVALE

TEMPORAL ARTERITIS

(Cranial Arteritis)

Temporal arteritis is a self limited febrile disease of unknown etiology in which the temporal arteries and occasionally other arteries of the cranial system are the seat of a necrotizing panarteritis. The active and symptomatic phase of the disease lasts from 2 to 3 months, after which recovery occurs although occlusion of the involved arteries usually persists. Relapses may occur and if visual impairment develops it is usually permanent.

Treatment of temporal arteritis has not been successful. Treatment of the active phase is mainly symptomatic and consists of the usual measures to relieve pain. Salicylates 15 grams (1 gm) three times daily and

CONTROL OF DIABETES The exact status of the diabetes should be determined and should be kept under rigid control. Since tissues of diabetic patients are notoriously susceptible to infection and since infections in ischaemic feet and legs may be disastrous the control of the diabetes is especially important particularly in those who have arterial disease.

CONTROL OF FORTIFICATION. Polycythemia vera frequently leads to increased thrombosis in both arteries and veins. To arrest any progress of the underlying arterial disease it is evident that polycythemia if it exists should be treated and controlled.

ANTICOAGULANTS. Heparin and dicumarol are not of much practical value in the prevention of thrombosis in chronic occlusive arterial diseases because of the difficulty of safe administration over long periods and the uncertainty as to when the next episode of thrombosis may occur. If the patient is confined to the hospital however their use may be justified as 10 per cent of all patients will at some time during the course of their disease suffer from an acute arterial occlusion (Allen, Kvale and Allen).

Procedures Used for Vasodilatation. **WARM ENVIRONMENTAL TEMPERATURE.** One of the best procedures for maintaining vasodilatation is to place the patient in an environmental temperature of 80 to 85° F. The use of a heated box in which the patients extremities are protected from the heating elements and in which the temperatures do not exceed 90° F. is another aid in producing vasodilatation (Allen, Barker and Himes).

TABLE III

PROCEDURES USED FOR VASODILATION

- (1) Warm environmental temperature general and local
- (2) Heat or diathermy to uninvolved parts of the body
- (3) Intravenous administration of foreign protein (thyroid vaccine)
- (4) Intravenous administration of hypertonic sodium chloride solution
- (5) Ethyl alcohol by mouth
- (6) Papaverine
- (7) Administration of sympathetic nerves or ganglia
- (8) Tetra-ethyl ammonium chloride
- (9) Regional sympathetic ganglionectomy

that the patient remain in bed for a few days and soak the toe in warm water two or three times a day.

Corns and calluses should not be cut. Local applications for the removal of corns and proprietary corn and callus removers should never be used. It is much more important to select properly fitted shoes to overcome these deformities and when they do occur to apply corn pads and bunion pads to prevent pressure or to soak the foot in warm water several times a day to soften up the lesion and then gently remove the thick cornified layer of skin.

Chiroprody may be necessary in some cases but it should be done only by a competent chiropractor who has knowledge of the problems associated with occlusive arterial diseases. Injudicious surgical treatment of such lesions often leads to painful ulcers which are difficult to heal.

Exposure to excessive cold and excessive heat should be avoided. Ice should never be allowed to come in contact with an ischaemic extremity. Electric pads and hot water bottles should never be used no matter how cold the feet become. Such applications frequently result in painful ulcers which may take months to heal or never heal.

The patient should be cautioned against the hazards of trauma. At times this may be unavoidable. If trauma does occur and there is even the slightest break in the skin the patient should be cautioned against the use of a strong antiseptic such as tincture of iodine. All ointments or solutions containing phenol should be avoided.

FEVUS CONTROL. Thrombophlebitis should be treated by only the blandest of remedies. Irritating ointments and solutions should never be used. Potassium permanganate in a 1:9000 solution used to soak the feet twice a day is a safe and effective remedy. Acupuncturing the feet dry by bland dusting powders is advisable.

CONTROL OF LIPIDEMIA. The control of lipids in the presence of arteriosclerosis obliterans is not satisfactory at the present time. The low fat, low cholesterol diet is of questionable value may not be effective and may be difficult to adhere to for long periods. Thyroid in subtoxic doses may be effective and choline chloride has been found of value in some instances.

HEAT OR DIATHERMY TO UNINVOLVED PARTS OF THE BODY Vasodilatation can be produced by short wave diathermy applied to the trunk but it does not persist after the treatment has been discontinued and the method is therefore of limited value (Ben nett et al)

INTRAVENOUS ADMINISTRATION OF FOREIGN PROTEIN The injection of a foreign protein can be a valuable procedure for producing temporary vasodilatation and also for relieving pain, but it should be used only in thromboangitis obliterans (Barker) We prefer typhoid vaccine because of its availability, relatively standard strength, and ease of administration Any stock typhoid vaccine may be used and is administered intravenously two or three times a week. The first dose is usually 0.1 cc of the vaccine and this dose should be increased 0.1 cc with each subsequent injection, depending on the severity of the reaction

INTRAVENOUS ADMINISTRATION OF HYPER- TONIC SODIUM CHLORIDE SOLUTION This method of treatment is still being used in some eastern clinics, but our experiences with it have not been encouraging Two hundred and fifty to 300 cc of a 3 to 5 per cent solution may be administered two to three times a week

ETHYL ALCOHOL BY MOUTH Alcohol by mouth will cause significant vasodilatation but its effect is somewhat transient We use it almost routinely on all patients who are confined to the hospital for relief of pain and for sedation as well as for vasodilatation However, care should be taken that its use does not become an abuse, 2 ounces of whiskey two or three times daily is usually adequate

PAPAVERINE This drug is of little value when taken by mouth When used intravenously, 1½ grains (0.1 gm), is particularly helpful in releasing arterial spasm

ANESTHETIZATION OF SYMPATHETIC NERVES OR GANGLIA As an agent in the treatment of occlusive arterial diseases, anesthetization of sympathetic nerves or ganglia is of limited value because the effect is too transient It is, however, of value in testing for the degree of possible vasodilatation

TETRA-ETHYL AMMONIUM CHLORIDE In our experience, this drug is of little value in treatment but again it may be of use in test-

This operation is gaining in favor as treatment for arteriosclerosis obliterans as well as for thromboangitis obliterans Reasons are that the vasodilatation produced is essentially permanent and improvements in surgical technique have significantly reduced the surgical mortality rate and even morbidity The operation abolishes not only vasoconstriction but also sweating of the extremity, thus preventing excessive cooling of the skin as the result of evaporation of sweat Sympathectomy does not open arteries already occluded by an organic process and does not prevent the development of new occlusive lesions in arteries or veins, but it does provide maximal arteriolar dilatation, prevents secondary arteriolar spasm, which may occur after an acute arterial occlusion, and prevents gangrene in many patients It is by no means, however, a certain guarantee against gangrene

Sympathectomy should not be done in all cases of chronic occlusive disease In mild cases in which sufficient collateral circulation has developed over a period of years, the operation may not be justified In the more severe cases in which there is extensive ulceration or gangrene of the digits or of the foot and severe arterial insufficiency is present sympathectomy will be of little or no benefit In arteriosclerosis obliterans, care must be exercised in selecting the treatment, since in many instances the surgical risk is increased because of vascular lesions elsewhere in the body, particularly in the coronary and cerebral arteries, and because arterial thrombosis in the extremities may occur during the immediate postoperative period

Mechanical Methods for Increasing Circulation The Pavex alternating suction and pressure machine was in favor shortly after its introduction several years ago (Herrmann) but at present has been almost abandoned We have discarded its use altogether

The intermittent venous compression apparatus likewise held favor for several years, but it is of doubtful rationale and is being used less and less

The Sanders oscillating bed, which is merely a modification of the old postural

HEAT OR DIATHERMY TO UNINVOLVED PARTS OF THE BODY Vasodilatation can be produced by short wave diathermy applied to the trunk but it does not persist after the treatment has been discontinued and the method is therefore of limited value (Ben nett et al)

INTRAVENOUS ADMINISTRATION OF FOREIGN PROTEIN The injection of a foreign protein can be a valuable procedure for producing temporary vasodilatation and also for relieving

relatively standard strength and ease of administration. Any stock typhoid vaccine may be used and is administered intravenously two or three times a week. The first dose is usually 0.1 cc of the vaccine and this dose should be increased 0.1 cc with each subsequent injection depending on the severity of the reaction.

INTRAVENOUS ADMINISTRATION OF HYPER TONIC SODIUM CHLORIDE SOLUTION This method of treatment is still being used in some eastern clinics but our experiences with it have not been encouraging. Two hundred and fifty to 300 cc of a 3 to 5 per cent solution may be administered two to three times a week.

ETHYL ALCOHOL BY MOUTH Alcohol by mouth will cause significant vasodilatation but its effect is somewhat transient. We use it almost routinely on all patients who are confined to the hospital for relief of pain and for sedation as well as for vasodilatation. However care should be taken that its use does not become an abuse. 2 ounces of whiskey two or three times daily is usually adequate.

PAPAVERINE This drug is of little value when taken by mouth. When used intravenously 1½ grains (0.1 gm) is particularly helpful in releasing arterial spasm.

ANESTHETIZATION OF SYMPATHETIC NERVES OR GANGLIA As an agent in the treatment of occlusive arterial diseases anesthetization of sympathetic nerves or ganglia is of limited value because the effect is too transient. It is however of value in testing for the degree of possible vasodilatation.

TETRA ETHYL AMMONIUM CHLORIDE In our experience this drug is of little value in treatment but again it may be of use in test-

ing for possible vasodilatation in a dose of 1 cc (10 gm) intravenously.

REGIONAL SYMPATHETIC GANGLIOECTOMY This operation is gaining in favor as treatment for arteriosclerosis obliterans as well as for thromboangiitis obliterans. Reasons are that the vasodilatation produced is essentially permanent and improvements in surgical technique have significantly reduced the surgical mortality rate and even morbidity. The operation abolishes not only vasoconstriction but also sweating of the extremity thus preventing excessive cooling of the skin as the result of evaporation of sweat. Sympathectomy does not open arteries already occluded by an organic process and does not prevent the development of new occlusive lesions in arteries or veins but it does provide maximal arteriolar dilatation prevents secondary arteriolar spasm which may occur after an acute arterial occlusion and prevents gangrene in many patients. It is by no means however a certain guarantee against gangrene.

Sympathectomy should not be done in all cases of chronic occlusive disease. In mild cases in which sufficient collateral circulation has developed over a period of years the operation may not be justified. In the more severe cases in which there is extensive ulceration or gangrene of the digits or of the foot and severe arterial insufficiency is present sympathectomy will be of little or no benefit. In arteriosclerosis obliterans care must be exercised in selecting the treatment since in many instances the surgical risk is increased because of vascular lesions elsewhere in the body particularly in the coronary and cerebral arteries and because arterial thrombosis in the extremities may occur during the immediate postoperative period.

Mechanical Methods for Increasing Circulation The paver alternating suction and pressure machine was in favor shortly after its introduction several years ago (Herrmann) but at present has been almost abandoned. We have discarded its use altogether.

The intermittent venous compression apparatus likewise held favor for several years but it is of doubtful rationale and is being used less and less.

The Sanders oscillating bed which is merely a modification of the old postural

exercises carried out by the patient seems to be helpful in many cases and is still being used by us. It can be used for several hours each day or continuously for days or weeks. There is no evidence that it produces vaso dilatation but it seems to be helpful in some cases of severe ischemia. In our experience patients have obtained more relief from pain from this apparatus than from any of the other mechanical methods. Any of the three are at best only a supplement to other forms of treatment.

TABLE IV

MECHANICAL METHODS FOR INCREASING CIRCULATION

- (1) Intermittent suction and pressure
- (2) Intermittent venous compression
- (3) Oscillating bed

Control of Pain. The pain of intermittent claudication may be relieved in about 50 per cent of patients by the intramuscular injection of tissue extracts. Their use may not be justified however in all cases of occlusive arterial disease when the sole symptom may be intermittent claudication since the patient's occupation may not require excessive walking and the distance that he can walk may be sufficient so as not to interfere with his activities. When relief from intermittent claudication is desired however intramuscular injections of tissue extract may be used and may be successful. Of the tissue extracts we use pancreatic tissue extract. A specific plan of treatment varies but it is usually our custom to give 1 cc of deproteinized pancreatic tissue extract intramuscularly daily for 2 or 3 weeks then three times a week for the next 3 weeks and twice a week for another 3 weeks. After a rest period of 1 or 2 months such a course of treatment can be repeated if it is considered necessary. The use of tissue extracts alone in the treatment of pain of ischemic neuritis is ordinarily unsuccessful but it is generally used for this pain in conjunction with other forms of treatment.

Many drugs have been used for relief of the various types of rest pain whether associated with ulcerative or gangrenous lesions or with the excruciating pain of ischemic neuritis. These drugs are listed in Table V. Aspirin 10 grains (0.6 gm.) together with

whisky may frequently afford as much relief from pain as any of the other drugs. If opiates is not common but the possibility must be kept in mind always and the use of opiates must be kept at a minimum. Barbiturates such as 0.1 gm of secenal may be used as necessary for the induction of sleep but it may be ineffective if pain is severe. Generally the best plan is to get along as well as possible with as small amounts of the drug as possible and to discontinue its use when feasible.

TABLE V

CONTROL OF PAIN

- (1) Tissue extracts
- (2) Barbiturates
- (3) Salicylates
- (4) Opiates
- (5) Demerol hydrochloride
- (6) Ethyl alcohol by mouth
- (7) Anesthetization of peripheral nerves or nerve roots with alcohol or dolamine
- (8) Surgical section or crushing of peripheral nerves

In some cases of ischemic neuritis benefit has been obtained by the injection of dolamine into peripheral nerves or sensory nerve roots although experience is insufficient for adequate evaluation of this procedure to date. Injection of alcohol into nerve roots or peripheral nerves is not advisable though it has been advocated by Smithwick and White and by Scott and Morton. Surgical section or crushing of peripheral nerves in the lower third of the leg (Laskey and Silbert) would seem to be a rational procedure for the relief of intractable pain in the foot or toes but results generally have been rather disappointing. There is always the risk of nonhealing of the surgical incisions and if the pain is the result of ischemic neuritis section of the nerves in the region of the ankle will not relieve pain resulting from degeneration and fibrosis of nerves proximal to this point. Our experience with these methods of treatment has generally been unsuccessful and it has usually been necessary to amputate the leg in the cases in which they have been used particularly when

ceration or gangrene of one or more of the toes, or the foot, has been present

Treatment of Ulceration and Gangrene
The best treatment for ulceration and gangrene, as has already been mentioned, is, of course prevention. This cannot be overemphasized. It is still rather discouraging to realize that 50 per cent of all types of ulcerations and gangrene seen in arteriosclerosis obliterans and thromboangitis obliterans might have been prevented by avoidance of mechanical, chemical, and thermal trauma. Minor avoidable injury, hot water bottles or heating pads, ice packs, strong antiseptics, corn cures, keratolytic agents, and irritating ointments or solutions are strongly contraindicated for ischemic tissues.

TABLE VI

TREATMENT OF ULCERATION AND GANGRENE

- (1) Prophylaxis: avoidance of mechanical, thermal and chemical trauma
- (2) Fungus control
- (3) Warm soaks: bland solutions
- (4) Wet dressings: bland solutions
- (5) Ointments
- (6) Tyrothricin locally
- (7) Sulfonamides orally
- (8) Parenteral penicillin
- (9) Powdered erythrocytes
- (10) Débridement of gangrenous tissue
- (11) Amputation of digits
- (12) Amputation of limb

The patient with gangrene or ulceration should usually be treated in the hospital. One of the most important rules in the treatment of these lesions is to do as little as possible and to avoid any procedure which may have even the slightest possibility of producing more injury to tissue. It is best to keep the patient constantly in bed with the leg in a horizontal position as much as possible. Prolonged dependency of the leg may lead to edema and increased difficulty in healing. Many patients with constant pain tend to keep the affected leg hanging over the edge of the bed, since this seems to afford them some relief from pain. This must be avoided or attempts at healing of the lesion will be unsuccessful.

Warm (100 to 105° F) soaks in boric acid solution or weak (1:9000) solution of potassium permanganate for 10 or 15 min-

utes two or three times a day are probably about as efficacious in combating the infection usually associated with ulceration or gangrene as any other remedy. The use of warm, but never hot, wet dressings may further facilitate drainage and hasten the loosening of sloughs. When wet dressings are used, it is well to allow the ulcer or area of gangrene to be exposed to the air for an hour or so every 3 or 4 hours to avoid the maceration of tissue.

Ointments are usually of little value. There are few external applications which are bactericidal or bacteriostatic and still are not irritating to ischemic tissues. An ointment containing 5 per cent sulfathiazole is not irritating and may be of some help in loosening an area of localized gangrenous or necrotic tissue.

Weak solutions of tyrothricin (0.05 per cent solution) are bactericidal for some organisms and have a tendency to stimulate the growth of granulation tissue and epithelium. This form of treatment may be alternated with other methods mentioned previously.

The oral administration of sulfonamides and parenteral administration of penicillin alternately or in combination have been used to treat and inhibit the infection in ulcerative and gangrenous wounds. The results of treatment with these drugs have been uncertain, but it seems to be the consensus that healing occurs more readily than before the use of antibiotics.

When the ulcers have become clean powdered erythrocytes can be applied. They have been effective in promoting healing in some cases. It is well to alternate the use of powdered erythrocytes with either warm boric acid soaks or boric acid packs. Encrustations may ensue after prolonged use of powdered erythrocytes, pocketing regions of pus which cannot drain until soaks or packs are used.

Occasionally, gentle débridement of a gangrenous toe or portion of a toe, once it has loosened, will expedite healing. This should be done only, however, after the gangrenous region has become well demarcated and has begun to separate spontaneously.

Amputation of a toe may be undertaken if the gangrene is limited to the toe, if the collateral circulation appears adequate, and if

there is no infection in the base of the toe. However, there is always the possibility that healing will not occur, that an ulcer will

necessary. As a rule, amputations of the three middle toes are more likely to be followed by healing than are amputations of the first and fifth toes. Amputations of toes are generally more successful in thromboangitis obliterans than in arteriosclerosis obliterans. Amputation of any finger in thromboangitis obliterans has always been successful. Parenteral antibiotic therapy before and after amputation has been of considerable help

and amputation of the leg will be necessary. Transmetatarsal amputations are rarely successful. If healing does occur, the remaining portion of the foot is rarely useful. The best sites for amputation are through the midcalf region and through the middle third of the thigh. The best test is for the surgeon to make his incision in the midcalf without a tourniquet. If adequate bleeding occurs and the muscles appear to be reasonably healthy, then amputation can be completed at that site. However, if little bleeding occurs and the muscles appear to be moribund, a

putations

Newer Drug Therapy of Questionable or Temporary Value In the last few years several new methods of medical treatment have been advocated enthusiastically for chronic occlusive arterial diseases. The results described by the proponents of these

TABLE VII

NEWER DRUG THERAPY OF QUESTIONABLE OR TEMPORARY VALUE

- (1) Intravenous ether
- (2) Histidine and vitamin C
- (3) Priscol
- (4) Vitamin E
- (5) Intra arterial histamine

methods have not been uniformly confirmed. Intravenous ether (Katz), histidine and vita-

min C (Wirtschafter and Widmann), and intra arterial histamine (Mufson), have been reported as improving the circulation. Weisman and Allen have been unable to show that either intravenous ether or histidine and vitamin C had any beneficial effect on the circulation. We have had limited experience with intra arterial histamine, but our results to date have been disappointing. Priscol or priscoline, 50 mg three times daily, has been shown to be a vasodilating drug (Grimson et al), but in our experience it has been rather ineffective in the treatment of occlusive arterial diseases. The good results reported from treatment of occlusive arterial disease with vitamin E have not, to our knowledge, been confirmed.

Summary The general principles to be used in treating occlusive arterial diseases have been grouped under the headings of (1) procedures used to arrest the progress of the disease, (2) procedures used for vasodilatation, (3) mechanical methods for increasing circulation, (4) efforts to control pain, and (5) treatment of ulceration and gangrene.

RICHARD M SHICA
WALTER F KYALE

REFERENCES

- Allen E V, and MacLean A R. Treatment of Sudden Arterial Occlusion with Papaverine Hydrochloride. Report of Case. *Proc Staff Meet Mayo Clin*, 10:216, 1935.
- Allen E V, Barker N W, and Hines E A. *Peripheral Vascular Diseases*. Philadelphia W B
- Barker N W. Danger of Gangrene of Toes in Thrombo-angitis Obliterans and Arteriosclerosis Obliterans. *JAMA*, 104:2147, 1935.
- Barker N W. Results of Treatment of Thrombo-angitis Obliterans for Foreign Protein. *JAMA*, 97:841, 1931.
- Bennett R L, Hines E A, Jr, and Krusen, F H. Effect of Short wave Diathermy on Cutaneous Temperatures of Feet. *Am Heart J*, 21:490, 1941.
- Berry, R L, et al. Use of Tetraethylammonium in

- Sympathetic Ganglionectomy *Am Heart J* 10 143 1934
- Collens W S and Wilensky N D *Peripheral Vascular Diseases Diagnosis and Treatment* Springfield Ill C C Thomas 1939
- Crimson A S et al *The Effects of Priscol (2 Benzyl 5 Imidazole HCL) on Vascular Diseases and Hypertension in Patients* *Surgery* 23 725 1948
- Herrmann L G *Passive Vascular Exercises and the Conservative Management of Obliterative Arterial Diseases of the Extremities* Philadelphia J B Lippincott 1936
- Katz R A Preliminary Report of Medical Treatment of Diabetic Ischemic Gangrene with Diethyl Ether *Proc Am Diabetes A (1946)* 469 1946
- Kvale W and Allen M V Sudden Arterial Occlusion in Thrombo-angitis Obliterans *Am Heart J* 12 453 1936
- Laskey N F and Silbert M Thrombo-angitis Obliterans Relief of Pain by Peripheral Nerve Section *Ann Surg* 98 55 1933
- Leary W V and Allen E V Intermittent Claudication as Result of Arterial Spasm Induced by Walking *Am Heart J* 22 719 1941
- Messinger W J Goodman E N and White J C Treatment of Thrombo-angitis Obliterans *Am J Med* 6 168 1949
- Mufson I A New Treatment for the Relief of Obliterative Diseases of Peripheral Arteries *Ann Int Med* 29 903 1948
- Samuels M S *The Diagnosis and Treatment of Diseases of the Peripheral Arteries* New York Oxford University Press 1940
- Sanders C E Cardiovascular and Peripheral Vascular Diseases Treatment by Motorized Oscillating Bed *JAMA* 106 916 1936
- Scott W J M and Morton J J Principles of Treatment in Common Arterial Diseases of Extremities *JAMA* 99 982 1932
- Silbert S Thrombo-angitis Obliterans (Buerger)

vascular disease Its occurrence is always associated with the possible loss of the involved extremity and of the patient's life as well for amputation necessitated by severely ischemic tissue and gangrene is not without risk

Arterial embolism ordinarily produces profound effects on the arterial circulation (McKechnie and Allen) Such effects appear less striking in acute arterial thrombosis but are nonetheless important The resulting ischemia is due in large part to spasm of the collateral arteries induced by the presence of the embolus or thrombus If such ischemia persists for more than a few hours the intima of blood vessels beyond the site of occlusion is injured to such a degree that thrombosis occurs upon release of the arterial spasm Thus if treatment is delayed or inadequate the ischemia which originally was caused by mechanical obstruction of an artery by an embolus or thrombus and by arterial spasm eventually is the result of more diffuse intravascular thrombosis

In some instances the cause of the sudden arterial occlusion is not clinically apparent even after all available information has been considered Fortunately rational treatment of the arterial insufficiency resulting from occlusion ordinarily is not dependent on an exact determination of the cause except when embolectomy may be indicated

There are three important "don'ts" in the treatment of sudden occlusion of the arteries of the extremities namely (1) don't delay active treatment (2) don't elevate the involved extremity and (3) don't subject it to heat which exceeds 90° F (35° C) (Allen) To delay treatment means a poor prospect of recovery in those instances in which recovery will not occur spontaneously Elevation of an extremity after sudden arterial occlusion and the local application of heat are ill advised procedures The former augments the ischemia by further diminishing the flow of blood to the extremity while the latter may cause burns which may contribute importantly to eventual loss of the extremity

It has been estimated that in approximately 50 per cent of cases of sudden arterial occlusion of the extremities gangrene will develop if nothing but the simplest conservative treatment is carried out Better under

Sensory Nerves of Lower Leg *Surg Gynec & Obst* 51 394 1930

- Weissman S J and Allen E V *Unpublished Data*
- Wirtschaffner Z T and Widmann H Elaboration of Histamine in Vivo in Treatment of Peripheral Vascular Disorders Preliminary Report *JAMA* 133 604 1947

SUDDEN ARTERIAL OCCLUSION

(Arterial Embolism and Acute Arterial Thrombosis)

Sudden arterial occlusion is one of the most catastrophic complications of cardio

standing of the abnormal physiologic processes involved and the use of methods to correct them have yielded far better results than were obtained a few years ago when treatment was directed mainly to the local problem. However it is difficult to evaluate critically the efficacy of individual agents because of the almost universal tendency to employ numerous measures in a justifiable endeavor to save the extremity.

The relief of pain and of arterial spasm and the reduction of the coagulability of the blood are important considerations in the active treatment of sudden arterial occlusion. Morphine sulfate $\frac{1}{4}$ gram (15 mg) should be given immediately to control pain. The involved extremity should be placed in a dependent position. When a leg is involved the head of the bed should be elevated; when an arm is involved the patient should be placed in the semi-Fowler position. The

and a cradle with the temperature not to exceed 90° F open at one end may be placed over it.

Because only part of the impairment of the arterial circulation is due to the primary occlusive process in the artery relief of the associated arterial spasm which may further compromise the circulation is of paramount importance. One of the best ways of accomplishing this is to increase the environmental temperature. The patient should therefore be placed in a room the temperature of which is approximately 90° F (32° C). Alcohol which is both an anti-spasmodic and an anodyne should be given as whiskey in amounts of 2 fluid ounces (about 60 cc) every 2 to 4 hours depending on the tolerance of the patient. Papaverine hydrochloride may be given intravenously or injected directly into the artery proximal to the site of occlusion. The usual dose of

lower part of the abdomen and the lumbosacral region has some value. Heat should never be applied directly to the involved extremity and except for preamputation anesthesia the use of refrigeration should be condemned for many limbs have been lost by the injudicious use of such procedures. Spinal anesthesia or paravertebral anesthetization of appropriate sympathetic ganglia with novocain hydrochloride may be effective. It may be necessary to repeat these procedures several times within 2 or 3 days if any response is to be maintained. General sympathetic block with tetraethyl ammonium chloride and allied substances has been advocated (Acheson and Moe) but we have not been impressed with the value of these drugs in the treatment of sudden arterial occlusion. Since they may induce profound hypotension their use in such cases would not seem to be without hazard. In our experience a warm room, the injection of papaverine, the use of whiskey and the Sanders bed have been almost uniformly adequate.

The use of anticoagulants has constituted one of the greatest advances in the treatment of thromboembolic diseases in recent years. They are needed in instances of sudden occlusion of arteries of the extremities to prevent propagation of the occluding thrombus or embolus to prevent extensive thrombosis of the collateral arteries and veins which may follow the release of the secondary vascular spasm and to prevent further thromboembolism during periods when such complications may be imminent. We use the two anticoagulants heparin and dicumarol. The former produces its effect on the blood promptly while the latter does not produce an effect on the blood for from 24 to 48 hours. We have used heparin both by continuous intravenous infusion and by intermittent intravenous injection. The latter method has impressed us as being much simpler and just as effective as continuous intravenous infusion. The use of depot heparin would be helpful but to date the

Additional measures for inducing peripheral vasodilatation may be employed. The Sanders oscillating bed may be helpful and should be used if available. The use of reflex heat by means of a baker over the trunk or diathermy with the pads applied to the

the side effects notably pain at the site of injection have precluded their use in many instances.

We inject 50 mg of an undiluted solution of heparin intravenously every 4 hours until the dicumarol has become effective. If the use of dicumarol is contraindicated the injections of heparin should be continued for several days.

An initial dose of 300 mg of dicumarol is given orally about the same time as the first injection of heparin. This is followed by 200 mg on the second day of treatment. The subsequent dosage of dicumarol is determined by the level of prothrombin in the blood. We attempt to maintain the prothrombin at about 20 per cent of normal. If it is more than 20 per cent 48 hours after the initial dose 100 or 200 mg of dicumarol are given and the same dose is repeated each 24 hours when the level of prothrombin is more than 20 per cent. Inasmuch as the administration of heparin may influence the prothrombin time the blood for this determination should be withdrawn not earlier than 3 hours after the last injection of heparin.

If the prothrombin in the blood decreases to less than 10 per cent of normal or if there is evidence of bleeding as a result of prothrombin deficiency vitamin K should be administered intravenously in doses of 36 or 72 mg depending on the apparent urgency of the situation. When bleeding occurs as the result of heparinization the intravenous injection of 50 mg of protamine may be indicated and in the event serious hemorrhage occurs during treatment with either heparin or dicumarol intravenous infusions of fresh whole blood should be given.

The medical treatment of sudden arterial occlusion may be summarized as follows: (1) give an opiate to relieve pain; (2) induce arterial relaxation by the use of whisky by mouth, an increased environmental temperature, the oscillating bed if available, and the intravenous or intra-arterial injection of papaverine hydrochloride; (3) diminish coagulability of the blood by the use of heparin and dicumarol. The constant attention of a physician is required until the situation is relieved or the unfortunate outcome is established.

If the afore mentioned procedures fail to produce significant improvement in the circulation within 8 or 10 hours surgical removal of the clot should be considered.

When embolectomy or thrombectomy is contemplated the use of dicumarol should be discontinued. However we favor the continued use of heparin in such cases and if the surgeon wishes he may inject heparin directly into the artery proximal to the site of arteriotomy as soon as the incision has been closed.

Ordinarily treatment with anticoagulant can be discontinued after 7 to 10 days. However in certain instances of recurrent embolic arterial occlusions associated with chronic auricular fibrillation it may be advisable to continue the use of dicumarol indefinitely if attempts to restore and maintain sinus rhythm with quinidine have been unsuccessful.

The subsequent treatment of an extremity rendered permanently ischemic as the result of a sudden arterial occlusion is the same as that of chronic occlusive arterial disease.

RICHARD M. SHICK
WALTER F. KALE

RAYNAUD'S DISEASE

The patient should be reassured regarding the absence of serious organic disease of the blood vessels as well as the loss of extremities which should never occur in Raynaud's disease. Adequate protection is of paramount importance. This includes the use of warm clothing especially fur lined mittens and in some instances ear muffs and lined galoshes. Moving to a warmer climate may be advisable in some cases. Anemia if present should be corrected as well as any other conditions which are debilitating to the patient.

Inasmuch as it is well known that nicotine produces vasoconstriction the use of tobacco may be expected to aggravate Raynaud's phenomenon and hence its use should be discouraged in patients with Raynaud's disease.

A variety of drugs has been advocated for use in Raynaud's disease. The mere enumeration of these would indicate of itself that there is no medical treatment of specific or even of great value. The judicious use of mild sedatives during periods of increased nervous and emotional stress may be of some benefit. Mild Raynaud's disease associated with the menopausal syndrome may

be benefited by the use of estrogenic substances and in occasional instances in which Raynaud's phenomenon is greatly aggravated during the menstrual period moderate relief of symptoms may follow the administration of these drugs. The use of thyroid in instances of hypometabolism may be advisable although the effects of this treatment on the vasospastic disturbance have not been impressive.

The use of nitrites, papaverine and similar vasodilating drugs seems to have little if any effect on the course of Raynaud's disease. The action of these drugs is transient and their effect is less impressive than that induced by the ingestion of alcohol. However the use of alcohol in this disease has its obvious limitations. The use of some of the newer adrenolytic, sympathicolytic and

little or no practical value in the treatment of Raynaud's disease. We have had no experience with the use of the hydrogenated derivatives of ergot (Bluntschli and Goetz) but we doubt that these drugs will prove to be of much benefit in this condition. The application of nitroglycerine ointment to the fingers of patients with Raynaud's disease may be of benefit in some instances but the effects of this treatment are variable and unpredictable and its use is purely palliative. Acetyl beta methylcholine (methylcholine) chloride iontophoresis has been of little or no benefit in our hands.

It is apparent from the foregoing discussion that medical treatment of Raynaud's disease is not satisfactory. About all that can be said in summary is that reassurance of the patient is important so that an anxiety state will not develop; that protection from the cold in every way possible is advisable; and that estrogenic therapy in the female may be tried when seemingly indicated.

Sympathectomy still remains the most satisfactory method of treatment in Raynaud's disease. However the amount of disability resulting from the angiospastic disturbance should be considered carefully in the selection of patients for this procedure. Sympathectomy would be ill advised in the mild and nonprogressive type of the disease.

In the moderately advanced stage of the disease it is advisable for the patient to try a season or two in a warm climate if possible before undergoing sympathectomy. As much as some of these patients may live fairly comfortably for years in a mild climate. In the advanced stages of the disease in which painful superficial ulcers have developed on the tips of the fingers sympathectomy is justifiable and may be expected to result usually in the healing of the lesions and relief of pain. This procedure however may not prevent the subsequent recurrence of trophic lesions or development of scleroderma.

Sympathetic ganglionectomy with trunk resection is the operation usually performed at the Mayo Clinic (Allen Barker and Hines). The reason why lumbar sympathectomy generally produces more satisfactory results than cervicothoracic sympathectomy for Raynaud's disease is not clearly understood. It may be because Raynaud's phenomenon and trophic changes are not as severe in the feet as in the hands or because of inherent difference in the reaction of the blood vessels or the vasomotor nerves in the lower and upper extremities. There is evidence which suggests that preganglionic resections are more satisfactory than postganglionic resections although this point is still debatable. Sympathectomy may be of temporary benefit in scleroderma with associated Raynaud's phenomenon. However in our experience this procedure generally does not alter the course of the primary disease and is recommended only in cases in which the vasospastic disturbance is severe and incapacitating.

The painful ulcers which develop on the tips of the fingers of some patients with advanced Raynaud's disease are treated in much the same manner as the ischemic ulcers associated with thromboangitis obliterans.

RICHARD M. SHICK
WALTER F. KNALE

LIVIDO RETICULARIS AND ACROCYANOSIS

Livedo reticularis is a vasospastic disorder characterized by a persistent bluish to bluish red mottling of the skin of both legs and feet which is more prominent on ex-

posure to decreased environmental temperature. The mottling involves the hands and arms to a less degree and may extend to the thighs and even the lower part of the trunk. Ordinarily the condition is asymptomatic although some patients complain of coldness, numbness, paresthesias and dull aching of the feet and legs. In severe cases ulcers may develop on the skin of the legs and in rare instances gangrene of the toes as the result of occlusion of the digital arteries has been observed.

Although in most of the cases of livedo reticularis no treatment other than reassurance is required, the avoidance of exposure to cold so far as possible and abstinence from the use of tobacco may be indicated in some instances. A period of rest in bed together with medical and physical vasodilating procedures is advisable when ulceration or gangrene is present. Sympathectomy has been employed with some success in a few cases.

Acrocyanosis is a vasospastic condition characterized by painless and persistent coldness and cyanosis of the distal parts of the extremities and is closely allied to livedo reticularis. The mechanism producing the vascular changes in these two conditions is not clearly understood but is generally considered to be that of arteriolar constriction with associated dilatation of the capillaries and venules. Whether these phenomena are due to some local fault in the smaller blood vessels or are the result of a hyperreactive sympathetic nervous system is still a debatable question.

The treatment of acrocyanosis has not been satisfactory. However, the condition is usually so innocuous that protection from cold is the only treatment necessary. The use of acetyl beta methylcholine (mecholyl) chloride by iontophoresis has been advocated but in the majority of cases this is not necessary. In the rare severe cases sympathetic ganglionectomy may be considered.

RICHARD M. SHICK
WALTER F. KVALE

ERYTHROMELALGIA

(Erythromalgia)

Erythromalgia is an uncommon vascular disorder characterized by intermittent burn-

ing pain associated with redness and increased warmth of the skin of the extremities. The feet are usually involved and the symptoms are induced by exposure to increased environmental temperature, are intensified by prolonged dependency and are relieved by cooling the affected parts.

Erythromalgia may occur primarily in the idiopathic type or it can occur secondarily in association with a number of conditions and diseases, notably polycythemia vera and hypertension. It has also been observed in cases of gout, organic neurologic disease and poisoning from thallium mercury or arsenic.

The treatment of erythromalgia is not uniformly successful. When the syndrome is secondary to some other condition the treatment is that of the condition which produces it. Of course the importance of avoiding anything that produces vasodilatation in the extremities should be emphasized. Light weight shoes and socks or stockings should be worn and exposure to warm environmental temperature should be minimized. Change of residence to a moderate climate may be advisable.

Desensitization of the skin to warmth has not proved to be of much help in our experience. However, this method of treatment seems rational and probably warrants further trial. Desensitization is begun by immersing the involved extremities in water at 30° C for 15 minutes twice daily for 2 or 3 days. The temperature of the water is then increased 1 or 2° for another period of 2 or 3 days and this program is continued. If symptoms occur when the temperature of the water is that which ordinarily provokes distress, the course of desensitization is repeated.

For reasons not clearly understood, as little as 10 grains (about 0.65 gm.) of acetyl salicylic acid may produce marked relief which may persist for as long as several days. Relief has been noted following the injection or inhalation of solutions of epinephrine hydrochloride (Mufson) but we have not had much experience with this form of treat-

necessary to anesthetize the skin of the feet by section or crushing of the appropriate

peripheral nerves or by the injection of alcohol into them Sympathectomy also may be considered if relief of the distress is obtained by anesthetization of appropriate sympathetic nerves

RICHARD M SINICK
WALTER F KVALE

REFERENCES

- Acheson G H and Moe G K Action of Tetraethyl ammonium Ion on Mammalian Circulation *J Pharmacol & Exper Therap* 87 220 1946
- Acheson G H and Moe G K Some Effects of Tetraethyl Ammonium on Mammalian Heart *J Pharmacol & Exper Therap* 84 189 1945
- Ahlquist R H Huggins R A and Woodbury R A Pharmacology of Benzylmethylazoline (Pnscol) *J Pharmacol & Exper Therap* 89 271 1947
- Allen E V Personal Communication
- Allen E V Emergency Treatment of Vascular Occlusions *JAMA* 135 15 1947
- Allen E V Barker N W and Hines E A Jr *Peripheral Vascular Diseases* Philadelphia W B Saunders Company 1946
- Barker N W Hines E A Jr and Craig W M Livedo Reticularis Peripheral Arterial Disease *Am Heart J* 21 592 1941
- Blumstahl H J and Coetz R H Effect of Ergot Derivatives on Circulation in Man with Special Reference to 2 New Hydrogenated Compounds (Dihydroergotamine and Dihydroergocornine) *Am Heart J* 35 873 1948
- For M J and Leslie C L Treatment of Raynaud's Disease with Nitroglycerine *Wisconsin M J* 47 855 1948
- Grimson K S et al The Effects of Pnscol (2-Benzyl-4,5-Imidazoline HCl) on Peripheral Vascular Diseases Hypertension and Circulation in Patients *Ann Surg* 129 968 1948
- Kovacs J Iontophoresis of Acetyl beta methylcholine Chloride in Treatment of Chronic Arthritis and Peripheral Vascular Disease *Am J M Sc* 183 32 1954
- Lewis T Clinical Observations and Experiments Relating to Burning Pain in Extremities and to So-called "Erythromelalgia" in Particular *Clin Sc* 1 175 1953
- Loewe L Rosenblatt P and Hirsch E Venous Thromboembolic Disease *JAMA* 130 386 1946
- Lund F Percutaneous Nitroglycerine Treatment in Cases of Peripheral Circulatory Disorders Especially Raynaud's Disease *Acta med Scand nav* 206 196 1948
- McKechnie R E Jr and Allen E V Effect on

terized by Redness Heat and Pain. *Am Heart J* 16 175 1938

Wright I S *Vascular Diseases in Clinical Practice* Chicago Year Book Publishers 1948

SCLERODERMA

(Acroscleroderma Acrosclerosis Diffuse Scleroderma)

Scleroderma is characterized by induration of the skin frequently associated with atrophy and pigmentation vasomotor disturbances and at times myosclerosis and calcinosis Three distinct types occur diffuse scleroderma acroscleroderma with Raynaud's phenomenon (acrosclerosis), and circumscribed scleroderma (morphea) Sclerodactylia which may develop in association with advanced Raynaud's disease of long standing is considered by some observers to be secondary to the circulatory disturbance and by others to be part of the syndrome of acrosclerosis

Scleroderma may involve any area of the surface of the body and also various visceral organs notably the esophagus and lungs However our remarks will be confined chiefly to acrosclerosis which is a syndrome characterized by scleroderma of the extremities face and thorax associated with Raynaud's phenomenon in the extremities and includes instances of primary sclerodactylia

In the treatment of scleroderma palliative measures may be of considerable value These measures are essentially the same as those employed in cases of Raynaud's disease without scleroderma and include (1) protection of the diseased portions against trauma and extreme environmental temperatures and (2) increase of peripheral circulation It is also important to increase the suppleness of the involved parts in order to delay hardening and contracture of the skin and subcutaneous tissues This is accomplished mainly by the use of physical therapy including heat and massage and the judicious use of contrast baths Emotional and psychic stresses should be avoided and the use of tobacco should be discouraged

The use of thyroid, pancreatic preparations and injections of posterior pituitary extract has been advocated (Oliver and Lerman) Our experiences with the use of these preparations as well as mecholy-

chloride by iontophoresis have been uniformly discouraging (Duryee and Wright). Prostigmine (neostigmine) may be of some benefit in increasing strength and a sense of well being and in mobilizing the stiffened muscles and joints in patients with mild or moderately advanced atherosclerosis. The use of this drug both intramuscularly, 0.5 mg three to four times daily, and orally, 15 mg four times daily, in conjunction with papaverine, 0.1 gm, seems to be of value in some cases (O'Leary).

The administration of the antihistaminic drugs in increasing doses to the limit of tolerance may be of some value in the early and edematous phases of the disease, and results with the use of androgens in a small group of cases have been somewhat encouraging to date. Other methods of treatment of no or questionable value include the use of gold or bismuth, alpha tocopherol (vitamin E), dihydrotachysterol (AT 10), and the local application of various agents, including nitroglycerin ointment (Kierland).

Sympathectomy has been of limited benefit in the treatment of scleroderma. The following situations may be considered in indications for this procedure: (1) minimal and slowly progressive atherosclerosis with associated Raynaud's phenomenon of moderate degree; (2) moderate atherosclerosis with severe spasmodic pain in the fingers as the result of frequent and severe attacks of vasospasm (Raynaud's phenomenon), and (3) slight or moderately severe sclerodactylia with recurring painful fissures and ulcerations that have not responded to more conservative methods of vasodilatation. Parathyroidectomy has been recommended on the ground that some disturbance of calcium metabolism may play a part in the pathogenesis of this disease. This operation has largely been abandoned as useless in scleroderma.

There is some reason to believe that the adrenal cortical hormone, 17-hydroxy 11 dehydrocorticosterone (compound E), and pituitary adrenocorticotrophic hormone (ACTH) may prove to be of value in the treatment of scleroderma and allied conditions (Hench et al).

RICHARD M. SHICK
WALTER F. KVALE

REFERENCES

- Allen, E. V., Barker, N. W., and Hines, E. A. Jr. *Peripheral Vascular Diseases*. Philadelphia: W. B. Saunders Company, 1948.
- Duryee, A. W., and Wright, I. M. Treatment of Scleroderma by Means of Acetyl Beta Methyl Choline Chloride (Mechoyl) Iontophoresis. *Am. Heart J.*, 14:603, 1937.
- Hench P. S., et al. Effect of Hormone of Adrenal Cortex (17-hydroxy-11-dehydrocorticosterone Compound E) and of Pituitary Adrenocorticotrophic Hormone on Rheumatoid Arthritis. Preliminary Report. *Proc. Staff Meet., Mayo Clin.*, 24:181, 1949.
- Hench P. S., et al. Effects of Adrenal Cortical Hormone 17-hydroxy 11-dehydrocorticosterone (Compound E) on Acute Phase of Rheumatic Fever. Preliminary Report. *Proc. Staff Meet., Mayo Clin.*, 24:277, 1949.
- Kierland R. R. Personal Communication.
- O'Leary, P. A. Personal Communication.
- O'Leary, P. A., and Waisman M. Atherosclerosis. *Arch. Dermat. & Syph.*, 47:382, 1943.
- Oliver, E. L., and Lerman, J. Scleroderma Treated with Injections of Posterior Pituitary Extract. *Arch. Dermat. & Syph.*, 34:469, 1936.
- Perlow, S. Prostigmine in Treatment of Peripheral Circulatory Disturbances. *J. A. M. A.*, 114:1991, 1940.

PHLEBOTHROMBOSIS AND THROMBOPHLEBITIS

The therapy of peripheral venous thrombosis has undergone many fundamental alterations during the past decade. The role of secondary vasospasm in the causation of the symptoms and the complications of peripheral venous thrombosis was first recognized by Albert and Leriche. The prevention of the formation of intravascular blood clots by the use of natural and synthetic anticoagulants was shown to be practical by Jorpes, Murray, and Link, while the localization of blood clots to an extremity by the ligation of large veins was first practiced by Homans and by Arthur Allen. These diverse methods of treatment have made available valuable data on which we have based our practical measures for the management of patients with peripheral venous thrombosis.

This discussion would be incomplete without a short summary of those important clinical aspects of the problem which must be kept in mind if the process of venous thrombosis and its complications are to be treated successfully.

General Considerations Massive pulmonary embolism which is the dreaded sequel of peripheral venous thrombosis, is a threat to the patient's life following any major surgical operation, any trauma to the extremities, any protracted serious illness, or at the termination of pregnancy. The physicochemical alterations in the blood which initiate such venous thromboses do not differ greatly from those incidental to the normal process of coagulation except that, under ordinary conditions blood does not clot within the normal blood vessels during life.

Many terms have been used to describe the various phases of venous thrombosis. The most commonly used terms are thrombophlebitis, phlebothrombosis, bland or silent venous thrombosis and just plain venous thrombosis. From the pathologic standpoint it is logical to assume that the simplest variety of venous thrombosis should be unassociated with inflammation, consequently the clot will be loosely attached to the wall of the vein. Such a condition has been called *phlebothrombosis* (Ochsner and DeBakey). On the other hand, the intravascular clotting of blood associated with and dependent on inflammatory changes in the wall of the vein, with the clot usually firmly attached, has been called *thrombophlebitis*. There are numerous phases to the reaction in the wall of the vein after intravascular clotting of blood takes place. Bland intravascular clots may extend from the deep veins of the leg into the iliofemoral segments where perivenous reaction to the clot may

the right side of the heart, should not be overlooked as silent but important sources of blood clots which may be carried to the lungs and lodged as emboli. Massive pulmonary emboli often have their origin from such sites of thrombosis. The incidence of small latent blood clots in the pelvic veins, periprostatic, and perivesical plexuses is high and we believe such clots frequently initiate ascending venous thrombosis after slight trauma or after some physicochemical changes cause a sudden rise in the coagulability of the blood.

Pulmonary embolism has been considered by some clinicians as a catastrophe which makes its appearance without special warning in an otherwise healthy patient who has almost recovered from some surgical operation. Such a concept of pulmonary embolism is archaic, for it is well established that this complication of venous thrombosis is even more frequent in patients who have been confined to bed for some reason other than a surgical operation. This is particularly true of patients over 40 years of age who have been confined to bed because of chronic heart disease or fracture of some long bone of the body.

The important considerations for the clinician however, center around the prevention of the formation of blood clots within peripheral veins or, if they have already formed how they may be prevented from being extended or transported to vital parts of the body. The early recognition of peripheral venous thrombosis is therefore essential to effective therapy.

Prevention of Venous Thrombosis Prolonged stagnation of blood in the various venous plexuses of the body favors the formation of intravascular thrombosis. Many factors influence the return of blood from the peripheral veins. The maintenance of normal negative pressure within the abdomen and thorax with the elimination of all forms of mechanical obstruction to the return flow of blood must not be minimized. The muscles of the calf region are pressed against the mattress when patients lie in bed and there is abnormal pressure over the adductor regions in fat individuals whose thighs press together while lying in bed. It would be poor clinical judgment to give active treatment for a weak heart muscle and

the development of a bland, nonadherent thrombus extending proximally from such an area of thrombophlebitis. The differentiation, therefore, of thrombophlebitis from phlebothrombosis is largely of academic interest, for in clinical practice these two phases of venous thrombosis are frequently seen in the same patient at the same time.

Much has been written recently about the importance of the veins of the calf muscles as the main source of pulmonary emboli, yet clinical experience has indicated that other sources, especially the veins of the pelvis and abdomen, and particularly the chambers of

limiting the extension of venous thrombosis in the extremities

Antidotes for Heparin and Dicumarol

If an emergency operation is necessary while the clotting time is prolonged by the administration of heparin, the effect of the heparin can be neutralized immediately by the intravenous administration of protamine sulfate. One cubic centimeter of 1 per cent protamine sulfate solution will neutralize at least 15 mg of crystalline heparin.

If the prothrombin concentration is decreased by the administration of dicumarol, the effect of this drug can be abolished by the transfusion of freshly drawn citrated whole blood or by the intravenous administration of 40 to 60 mg of menadiolone bisulfate, or by the injection of Vitamin K₁ oxide.

Contraindications to Use of Anticoagulants The presence of any blood dyscrasia which produces a hemorrhagic tendency or any form of purpura is considered a contraindication to the use of either heparin or dicumarol. Patients with definite hepatic insufficiency or hepatogenous jaundice, especially if associated with prothrombin deficiency, should never be given dicumarol. Patients with renal insufficiency, active tuberculosis, open wounds, or potential bleeding surfaces should be given heparin or dicumarol with great caution. Dietary or nutritional deficiency should preclude the use of either heparin or dicumarol.

LOCAL DERANGEMENTS OF THE CIRCULATION Elevation of the extremity is the most effective means of reducing the edema of the tissues in patients with venous thrombosis. The high protein content of the lymphatic fluid from the nodular thrombophlebitic extremity makes it essential to keep the swelling at a minimal level lest the fluid clot and the resulting cellular reaction produce irreparable changes in the tissues.

Röntgen Therapy The pain of subacute and chronic phlebitis can be lessened and the edema reduced by small doses of roentgen irradiation. Doses of 200 r may give a serious general reaction in patients with acute phlebitis. Between 30 and 40 per cent of an erythema dose (125 to 135 r) with heavy infiltration may even cause some rise in temperature over the veins. For the most beneficial results in mild forms of thrombophlebitis, we recommend not more than 80 r

through filters of 2 mm of aluminum and 0.25 mm of copper, to be given at one week intervals.

Anesthetization of Regional Sympathetic Ganglia This procedure is commonly referred to as a "paravertebral block" and has been widely used to give relief of swelling and pain in the acute phases of thrombophlebitis. On the basis of experimental observations, Albert suggested the procedure to Leriche for clinical application. In 1934 Leriche and Kunlin described the method of blocking the regional sympathetic ganglia (I, II, III) with 10 to 15 cc of 1 per cent solution of procaine hydrochloride at each level, to overcome the secondary vasospasm associated with acute postoperative thrombophlebitis. Their reports indicate that most of their patients were relieved of their symptoms by this paralysis of the vasomotor nerves to the affected extremity. In 1939 Ochsner and DeBakey confirmed these results and suggested that the method of treatment be applied more widely.

Proper anesthetization of these ganglia will usually relieve pain, reduce the edema of the part, and restore the arterial pulsations to a normal level. The beneficial effects of this simple therapeutic procedure in the chronic phase of iliofemoral thrombophlebitis which has caused considerable chronic have been 100 of dis thrombophlebitis can usually be shortened by repeated anesthetization of the regional sympathetic ganglia.

PREVENTION OF TRANSPORTATION OF FRAGMENTS OF CLOT The interruption of the deep veins of an extremity to prevent transportation of fragments of a blood clot to the lungs is still not widely accepted.

In all cases of acute ascending venous thrombosis in the great saphenous vein of the thigh, the saphenous vein should be ligated and divided at its junction with the femoral vein before the process of thrombosis ascends to that level. Such superficial venous thrombosis usually ascends progressively and may enter the common femoral vein and produce signs of deep venous thrombosis. In the chronic forms of thrombophlebitis where the common femoral vein had previously been occluded, the added danger from ascending

thrombosis in the great saphenous vein is then slight.

In patients with *acute venous thrombosis* which involves the deep veins of the calf of the leg or a popliteal vein in which there is no evidence of periphlebitis or reflex vasomotor phenomenon indicating involvement of the iliofemoral segment the ligation and division of the superficial femoral vein are occasionally indicated. We prefer anticoagulants alone but if the venous thrombosis is ascending the combination of ligation of the superficial femoral vein and the use of anti-

We have not observed serious bleeding or

of peripheral venous thrombosis are most disabling and may be prevented by prolonged use of dicumarol

LOUIS C. HERRMANN

REFERENCES

after operation

Ligation of the inferior vena cava should be reserved for patients with suppurative thrombophlebitis or pyelephlebitis arising from disease in the pelvis

The common femoral veins the external iliac veins or the common iliac veins should not be ligated because the collateral venous circulation is so poor after the occlusion of these veins that chronic edema of the extremity usually results

PREVENTION OF RECURRENT ATTACKS Cardiac function must be kept efficient and all factors which produce stasis of blood in peripheral veins must be eliminated. Varicose veins should be removed by surgical operation and not obliterated by sclerosing solutions. Edema of the extremities must be controlled by properly fitted elastic stockings

We have found that the use of small doses of dicumarol (25 to 75 mg.) daily for many months has been indicated in some patients with recurrent attacks of venous thrombosis. Prothrombin time determinations are made at frequent intervals until the value becomes stabilized at about 50 per cent of normal

- Albert F. *Contribution à l'étude clinique et expérimentale des troubles vaso-moteurs "réflexes" d'origine traumatique*. Liège Belgium: Vaillant Carmanne 1924
- Allen A. W. Interruption of Deep Veins of Lower Extremities in Prevention and Treatment of Thrombosis and Embolism. *Surg., Gynec. & Obst.* 84:519 1947
- Austin F. B. and Herrmann L. G. Management of Venous Thrombosis and Pulmonary Embolism Following Injury to Extremities. *Am. J. Surg.* 76:586 1948
- Homans J. Thrombosis of Deep Veins of Lower Leg Causing Pulmonary Embolism. *New England J. Med.* 211:993 1934
- Jorpes J. E. Anticoagulant Therapy in Thrombosis. *Surg., Gynec. & Obst.* 84:877 1947
- Lenche R. Des réactions d'axe dans les traumatismes péripnéiques: importance de leur connaissance dans la chirurgie d'accident. *Rev. de chir. Paris* 62:579 1924
- Lenche R. and Kunlin J. Traitement immédiat des phlébites postopératoires par l'infiltration novocaïnique du sympathique lombaire. *Presse méd.* 49:1481 1934
- Link A. P. Anticoagulant Dicumarol (William Hamlin Wilder Memorial Lecture). *Proc. Inst. Med. Chicago* 15:370 1945
- Murray G. D. W. Hepatic in Surgical Treatment of Blood Vessels. *Arch. Surg.* 40:307 1940
- Ochsner A. and DeBakey M. Treatment of Thrombophlebitis by Novocain Block of Sympathetics. *Technique of Injection Surgery* 5:491 1939
- Ochsner A. and DeBakey M. Thrombophlebitis and Phlebothrombosis. C. Jeff Miller Lecture. *South Surgeon* 8:269 1939

daily Use of injectable liver extracts containing added pteroylglutamic acid is not recommended because of the small amount of pteroylglutamic acid given the patient, particularly in maintenance therapy when a single injection is administered only once a month

It is probable that within a short time, vitamin B₁₂ (possibly synthetic) or a microbially produced substance, probably identical with vitamin B₁₂ (Stokstad et al) will supplant liver extract in the treatment of pernicious anemia. Early reports indicate that these substances are fully effective in inducing and maintaining hematologic remission and in controlling the neurologic disorder. Vitamin B₁₂ in intramuscular doses of less than 0.005 mg daily or in single doses of as little as 0.003 mg have induced hematologic remission. Further study is necessary to establish proper dosage finally.

Although patients with pernicious anemia invariably have achlorhydria, the administration of hydrochloric acid to all patients is not required, and does not contribute to recovery from the anemia. However, any patient with achlorhydria may have digestive disorders which can be helped by the administration of acid. Thus, hydrochloric acid is indicated in patients with pernicious anemia only if symptoms of digestive disorder are present. Among these are either diarrhea or constipation, "gas in the stomach," belching, and sense of fullness after eating.

If it is used, hydrochloric acid should be given as the dilute USP preparation in doses of 2 to 5 ml well diluted in 150 to 200 ml of water, either 15 minutes before eating or taken with the meal. The acid causes some corrosion of teeth, both natural and artificial, so it should be ingested through a glass tube or straw and the mouth should be rinsed with water afterward.

Hydrochloric acid is available in tablet form as glutamic acid hydrochloride, each tablet being equivalent to 0.67 ml on being dissolved in the stomach. These tablets are less irritating to some patients than the solution of hydrochloric acid and are especially convenient when the patient is eating away from home. They are considerably more expensive than an equivalent amount of dilute hydrochloric acid.

Iron is of no value in the treatment of pernicious anemia, but it is not uncommon for patients with pernicious anemia to have iron deficiency in addition. This becomes manifest after the initial response with liver extract has been obtained. It is then observed that the hemoglobin increases more slowly than the erythrocyte count and determination of the indices shows values below normal for the mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration.

In this event iron therapy should be administered as described below. It should be borne in mind that the iron is being given to treat an iron deficiency anemia associated in this instance, with pernicious anemia. Iron is of no value in treating pernicious anemia itself.

In the presence of infection, such as cystitis or pyelitis, for example, the response to treatment is less rapid and less complete than in uncomplicated cases. The infection should be treated by the appropriate method and liver extract should be administered at more frequent intervals using the erythrocyte and hemoglobin levels as guides.

Macrocytic Anemia of Pregnancy. Pregnant women may develop a macrocytic anemia with megaloblastic hyperplasia of the marrow. These cases are uncommon in the author's experience. They respond well to therapy with either liver extract or pteroylglutamic acid (Moore et al). Since the latter is fully effective when given orally, it is probably the treatment of choice. It should be given in doses of 20 mg daily. Therapy can be discontinued when the pregnancy has terminated.

Much more common in pregnancy is a mild or moderate anemia, slightly macrocytic (mean corpuscular volume 100 to 105 cu microns), not associated with megaloblastic hyperplasia of the marrow. These patients will not respond to liver extract, pteroylglutamic acid, or other forms of therapy. The anemia is not severe enough to be serious and usually corrects itself within several weeks after termination of the pregnancy.

A bone marrow examination is essential, osis of true
associated
if the mar-

Macrocytic Anemia of Nutritional Deficiency Individuals eating inadequate diets presumably deficient in vitamin B₁₂ may develop macrocytic anemia associated with megaloblastic hyperplasia of the marrow. Such cases have been described by Spies in the mountain country of southern United States and sporadic cases associated with alcoholism, morphine addiction or other conditions limiting dietary intake are seen occasionally. Administration of an adequate diet will eventually produce recovery from the anemia. Administration of either liver extract or pteroylglutamic acid as in pernicious anemia permits of more rapid recovery however. When the anemia has been corrected and the patient is eating an adequate diet continued treatment is unnecessary.

Macrocytic Anemia of Infancy Macrocytic anemia with megaloblastic hyperplasia

infants fed solely or chiefly on certain proprietary milk substitutes which are presumably deficient in some hematopoietic substance. These infants also frequently show other evidence of malnutrition and often have mild infections which in themselves are not serious. The anemia responds well to pteroylglutamic acid (Zuelzer) while purified liver extracts and vitamin B₁₂ have been ineffective in at least some of the cases. Five to 20 mg daily cause rapid remissions to occur. Again unlike pernicious anemia continued treatment is unnecessary once the anemia has been corrected and a proper dietary regimen has been established. This includes the addition of supplemental foods to the diet in addition to diluted cow's milk or proprietary milk substitute.

Myxedema Hypothyroidism is commonly associated with anemia which is usually macrocytic but in which there is little varia-

administration of thyroid substance is followed by a slow improvement in the blood although complete restoration to normal may not occur for 3 to 12 months.

The simultaneous occurrence of pernicious anemia and myxedema has been observed (Wilkinson). In such cases neither liver ex-

tracts nor thyroid are effective when given alone but a good response is obtained when the two are given together.

ROBERT W. HEINLE
MARTIN EPSTEIN

APLASTIC AND PRIMARY REFRACTORY ANEMIA

Hypoplastic Anemia Hypoplastic (or aplastic) anemia may result from exposure to toxic agents or may occur without recognizable cause.

Hypoplastic anemia is especially apt to develop after exposure to benzene or compounds containing the benzene ring, certain of the heavy metals and certain drugs. These anemias are apt to be sudden in onset and rapidly progressive with marked thrombocytopenia and leukopenia in addition to the anemia.

There is no specific effective therapy. The offending agent should be removed. Liver extract, folic acid, iron or other such therapy has no beneficial effect. The patient should receive repeated transfusions with 500 ml of compatible blood given at intervals sufficiently close to maintain the erythrocyte count at around 3,000,000 per cubic millimeter.

Death in these patients is generally the result of hemorrhage associated with the thrombocytopenia. The hemoglobin is low.

count with multiple transfusions, minute hemorrhages into vital organs still cause death. There is no completely satisfactory manner to combat the bleeding tendency. Blood transfusions help to control it but the effect is not complete and is transient. Recently protamine and toluidine blue (Allen and Jacobsen) given intravenously have been claimed to have some effect. They can be given in doses of 2 to 3.5 mg per kilogram of body weight diluted in 500 ml of normal saline. While these compounds are efficient neutralizers of heparin, their effect in severe thrombocytopenias is doubtful and variable since hyperheparinemia probably is not a component of the bleeding tendency in these circumstances.

The leukopenia predisposes to infections.

which can usually be combated successfully with penicillin or the sulfonamides. It is desirable to administer penicillin prophylactically whether obvious infection is present or not. Intramuscular doses of 20 000 units of penicillin in aqueous solution at intervals of 3 hours or single doses of 300 000 units of one of the long acting preparations at intervals of 24 hours is recommended. Oral preparations given at intervals of 3 hours are satisfactory if the dose used is two to five times that of the intramuscular route.

While the great majority of these patients die within a short time blood transfusions should be administered steadily as long as life lasts since a small percentage finally makes a complete recovery.

Hypoplastic anemia also occurs without discernible cause. This is seen usually in older people (50 years of age and older). Its onset is slower and often the thrombocytopenia and leukopenia are not as marked. Again bleeding is the controlling factor and if this is absent as is not infrequently the case such patients can be kept alive for many years with repeated transfusions. It is desirable if feasible to administer single blood transfusions of 500 ml at weekly intervals after the patient has received enough blood to raise the erythrocyte level sufficiently to alleviate symptoms of anemia (between 3 000 000 and 4 000 000 per cubic millimeter). The regular transfusions of blood at short intervals maintain the blood at a fairly constant level and prevent the severe anemia which develops if several transfusions are given on consecutive days with long intervals between courses of transfusions.

Although such treatment may prolong life from a few months to several years thrombocytopenia ultimately develops and death occurs in spite of transfusions.

Achrestic Anemia Another refractory anemia described mainly in the British literature is the so called achrestic anemia. The incidence of this type of anemia in the United States is apparently low. While the blood and bone marrow findings resemble those seen in pernicious anemia there is no response to liver extracts. A questionable response has been observed after treatment with folic acid (Wilkinson). Blood transfu-

sions should be given as indicated by the degree of the anemia.

Myelophthisic Anemia This term is applied to the anemias associated with diseases involving the bone marrow such as leukemia lymphosarcoma Hodgkins disease and plasma cell (multiple) myeloma. In some of these the bone marrow is more than normally cellular owing to the presence of abnormal numbers of the pathologic cell. In other cases such as plasma cell myeloma the cellularity of the marrow is greatly decreased. In any event the resulting anemia is of the hypoplastic type and will not respond to therapy with liver folic acid iron or vitamins.

The primary disease should be treated as far as possible and in the chronic leukemias radiation therapy is followed by marked improvement in the anemia. Other than this blood transfusion is the only treatment. As in true hypoplastic anemia thrombocytopenia with the attendant hemorrhage is often an outstanding feature and may be fatal.

It should be emphasized that liver extracts pteroylglutamic acid iron vitamins and all other known medications are without benefit in any of the hypoplastic anemias discussed in this section and there is no rationale for their use.

ROBERT W. HEINLE
MARTIN EPSTEIN

HYPOCHROMIC ANEMIA

Iron Deficiency Anemia The great majority of hypochromic anemias are the result of insufficient iron stores. This occurs in infancy because of iron deficiency in the mother during pregnancy. Growth increases demand for iron so that anemia may develop in adolescence. It occurs in adult women as the result of excessive menstrual flow or increased demands for iron during pregnancy. It occurs in either sex at any age as the result of chronic blood loss. It should be emphasized that apart from pregnancy hypochromic anemia in the adult almost invariably represents blood loss. It is not always possible to demonstrate the site of bleeding at the time the patient presents himself since the bleeding may have stopped. Thorough search of the patient for possible

causes of hemorrhage especially cancer should be made. This includes roentgen studies of the lungs and gastro intestinal and urinary tracts if other methods of investigation fail to reveal a potential source of bleeding.

In treatment the bleeding should be eliminated by suitable procedures. Other than this treatment consists of the administration of inorganic ferrous salts by mouth. Practically any iron compound will be utilized in hemoglobin production if given in sufficient amount. Ferrous sulfate is probably the most popular preparation used although ferrous gluconate is gaining in popularity. Both have the advantages of being readily absorbed, less irritating to the gastric mucosa than many other iron salts and are inexpensive.

Either one should be used in doses of

ately after meals to obviate or decrease gastric irritation. In the case of ferrous sulfate enteric coated tablets are available and desirable.

There is considerable difference of opinion as to the necessity of hydrochloric acid for the absorption of iron. It is probable that iron is more readily absorbed in the presence of hydrochloric acid but good results are obtained in most patients with achlorhydria without the administration of acid.

The parenteral administration of iron is seldom if ever indicated and is undesirable because of the frequent occurrence of toxic reactions. In the event that orally administered iron cannot be tolerated or cannot be absorbed because of diarrhea as occurs in certain cases of ulcerative colitis for example blood transfusions are preferable to parenterally administered iron salts. In the event that intramuscular administration of iron is considered desirable iron and ammonium citrate is probably the safest and as effective a preparation as any. It should be started in small doses for example 10 mg the first dose 25 mg 2 days later 50 mg in another 2 days and then if no undesirable reactions result 100 mg given at intervals of 2 or 3 days. Any single dose should not exceed 100 mg.

Infection Chronic infectious diseases are associated with hypochromic anemia but will respond little or not at all to administration of iron salts. Treatment of the infection and administration of blood transfusions as indicated represent the only effective therapy.

Cancer Cancer likewise is often associated with hypochromic anemia. If blood loss has occurred from the site of the cancer administration of iron salts will cause some rise in the hemoglobin although it is frequently impossible to restore it to normal. More often the hemoglobin levels off at 9.5 to 10 gm per 100 ml and will not respond to further iron therapy. If it is desired to raise the hemoglobin level further blood transfusions must be used.

Miscellaneous Other hypochromic anemias usually the result of congenital or inherited defects also occur and are important.

these anemias are often accompanied by splenomegaly removal of the spleen does not have a beneficial effect on the anemia. The only indication for splenectomy is discomfort caused by the enlarged organ.

Substances Other than Iron in Treatment In general it should be emphasized that liver or liver extracts have no beneficial effect on iron deficiency anemias. Preparations containing mixtures of liver iron and sometimes vitamins are widely advertised. They are much more costly than simple iron salts and add nothing to the effect of the iron. Their use can only be considered ill advised "shot gun therapy".

While copper is undoubtedly necessary for the formation of hemoglobin it is probable contrary to certain published claims (Fowler and Barer) that copper deficiency does not exist in adults. True copper deficiency has been recognized rarely in children. There is no indication for the administration of copper to adults. Furthermore unlike iron salts which are not toxic in ther-

including molybdenum has been advocated (Neary). In the writer's opinion convincing

evidence that this augments the effectiveness of iron has not been presented

ROBERT W. HEINLE
MARTIN EPSTEIN

HEMOLYTIC ANEMIA

Congenital Hemolytic Anemia Congenital hemolytic anemia (also called congenital or familial hemolytic icterus) is a well defined syndrome associated with spherocytosis of the erythrocytes, splenomegaly, and bouts of jaundice and fever. Since it is congenital it is often recognized in infants and children. Mulder cases may escape detection until adult life, however, sometimes being diagnosed during a pregnancy when the obstetrician seeks an explanation for the presence of anemia.

Splenectomy is curative in these patients so far as the symptoms are concerned. While the congenital defect, spherocytosis, is not significantly altered after splenectomy, the abnormally shaped erythrocytes are no longer destroyed more rapidly than normally, so that excessive hemolysis stops and the blood values return to and remain permanently at normal levels.

Acute Hemolytic Anemia An acute hemolytic anemia, often called *Lederer's anemia*, most often occurs in infants or young children, although it has been observed in adults. As seen in children, it most commonly appears 1 to 2 weeks after a mild illness frequently an upper respiratory infection. The onset of the anemia is sudden and there may be a rapid drop in the erythrocyte count to low levels in a day or two.

Blood transfusions, are usually followed by rapid cessation of the hemolytic process. In many cases, a single blood transfusion is effective in causing improvement. More commonly three to six transfusions given at daily intervals or as frequently as necessary as judged by the degree of anemia, are required. Recovery is complete and relapses seldom occur. If the patient is a child, any single blood transfusion should consist of about 20 ml per kilogram of body weight.

Some cases have been observed to become chronic. Splenectomy has been said to have been of value in these patients, as in the occasional patient with the acute process

who does not respond to blood transfusions. There is some dispute about this, but since there is no treatment other than blood transfusions, splenectomy should certainly be offered to those patients who fail to respond after transfusions. The subject has been thoroughly reviewed by Damashek.

Hemolytic Anemia with Serum Agglutinins Other types of hemolytic anemia associated with spherocytosis of the erythrocytes are occasionally encountered. It has been claimed that abnormal serum agglutinins can be demonstrated in certain of these cases (Loutit and Morrison). The pathologic mechanism of the disorder is not understood and splenectomy is not of value. Supportive treatment with blood transfusions represents the only available therapy.

Sickle Cell Anemia (Thalassemia) Sickle cell anemia and Cooley's anemia (thalassemia, erythroblastic anemia) both involve excessive hemolysis of erythrocytes. In both diseases the erythrocytes are characteristically flatter than normal and contain small

amounts of hemoglobin. Splenectomy should be given as required by the degree of anemia present. In both diseases the spleen may become so large that splenectomy is justified in order to relieve symptoms produced by the size of the organ.

In sickle cell anemia anoxemia should be avoided since this increases the tendency for sickling of the erythrocytes and accelerates the rate of hemolysis. These individuals almost invariably develop hemolytic crises following inhalation anesthesia even though precautions to avoid anoxemia are taken. The crises so induced can usually be combated successfully by multiple blood transfusions since only the cells of the patient are hemolyzed, the transfused cells surviving in the recipient's blood a normal period of time.

Reactions to Transfusion with Incompatible Blood There are various types of secondary hemolytic anemias. One type results from the administration of incompatible blood, either on the basis of the A and B agglutinogens or because of the administration of Rh positive blood to Rh negative individuals who have been sensitized to the Rh factor with resultant production of anti-

bodies. In either case the diagnosis should be made quickly. As soon as any combination of symptoms including chill, fever, pain in the lower back or a sense of oppression in the chest is manifest the transfusion should be stopped immediately.

It has been customary to institute alkali therapy as promptly as possible. The free hemoglobin present in the blood precipitates as casts in the kidney tubules and it is well known that hemoglobin is more soluble in alkaline solutions than in acid. However, whether alkalinization of the urine actually prevents formation of hemoglobin casts in the kidney tubules and if it does whether the more important kidney insufficiency which results from lower nephron nephrosis is altered in any way is doubtful (Lucke). The clinical impression persists, however, that some benefit may be expected from alkalinization. A suitable plan includes the intravenous administration of 250 ml of M/6 sodium lactate with initial oral administration of 15 gm of sodium bicarbonate. During the next 24 hours oral doses of 5 gm of sodium bicarbonate should be given at intervals of 3 or 4 hours and the intravenous administration of sodium lactate can be repeated. The urine should be maintained at an alkaline pH of 7.0 or greater until the benzidine test for hemoglobin becomes negative usually 24 hours or less unless the nephrotic syndrome develops. In this event oliguria occurs with urine of low specific

greater than the urinary output. If parenteral fluids are used, excessive amounts of sodium chloride solutions must be avoided since sodium retention promotes edema. A solution of 5 per cent glucose is satisfactory.

Hemolytic Anemia Associated with Cold Agglutinins. Recently hemolytic anemia resulting from the presence of abnormal cold agglutinins in the serum has been described (Finland et al.). The cold agglutinins so called because they can be demonstrated only at temperatures lower than that of the body are especially apt to be found in the serum of patients with atypical nonbacterial ("virus") pneumonia although they are found occasionally in other patients. Although the spleen is usually palpably en-

larged, splenectomy is of no value in altering the course of the anemia. Blood transfusion is hazardous since the transfused erythrocytes are also destroyed by the patient's serum. Most patients eventually recover although deaths have been reported. If the anemia becomes so severe that blood transfusions are considered imperative, every effort must be made to keep the blood at body temperature (98.6° F, 37° C) during transfusion. This may be accomplished by placing hot water bottles around the con-

the blood is given must also be kept warm since the superficial surface veins used in transfusion have a temperature lower than 98.6° F (37° C). Even with these precautions transfusion is often followed by a severe hemolytic episode so that the erythrocyte and hemoglobin levels may be lower following transfusion than before.

The patient should be protected against chilling even after recovery. Chilling even by immersing the hands or arms in cold water can precipitate hemolytic crises.

Hemolytic Anemias Due to Drugs or Toxins. Certain drugs or toxins may be responsible for hemolytic reactions. These include the sulfonamides, certain coal tar derivatives and lead compounds. Phenylhydrazine and its derivatives cause hemolysis. In Italy the raw fava bean or its blossom may produce a severe hemolytic anemia in sensitized individuals. Infections with hemolytic streptococcus and staphylococcus and with malaria may be associated with hemolytic anemia. Withdrawal of the drugs or removal of other causes and administration of blood transfusions as dictated by the degree of anemia result in disappearance of the hemolytic process and recovery of the patient.

ROBERT W. HEINLE
MARTIN EPSTEIN

ERYTHROBLASTOSIS FETALIS (Hemolytic Disease of the Newborn)

The term erythroblastosis fetalis is used to identify an acute hemolytic disease of the newborn which may assume varying clinical forms: fetal hydrops, icterus neonatorum.

and congenital anemia of the newborn. This disease begins in utero, often resulting in stillbirths but may not be evident until after the first few days of the infant's life. Briefly stated, the sequence of events in the pathogenesis of erythroblastosis is as follows: the mother is Rh negative, her erythrocytes being devoid of the Rh factor of Landsteiner and Wiener; the father is Rh positive, and the fetus is Rh positive, having inherited the factor from the father. Fetal erythrocytes enter the maternal circulation by some mechanism as yet not clearly defined. This stimulates the production of anti Rh iso-antibodies in the mother which diffuse into the fetal circulation via the permeable placenta and produce within the fetus an antigen-antibody reaction, with hemolysis of erythrocytes, and other manifestations of the disease.

The physician is often required to discuss with his patient whether pregnancy is contraindicated by Rh factor incompatibility, or, if it has already occurred, whether it should be terminated. It is well known that an affected baby is not produced in all such cases. It is extremely rare for the first pregnancy to produce an erythroblastotic baby, and in many instances this does not occur even after multiple pregnancies. This is explained by several factors: (1) Not all Rh negative women respond to the Rh antigen with antibody production. (2) It is thought that the normal placental barrier in most women cannot be penetrated by Rh factor bearing erythrocytes. (3) 57 per cent of Rh positive men are heterozygous, which means that such individuals upon mating with an Rh negative female will have offspring half of whom are Rh negative and only half Rh positive.

To summarize this particular problem it has been calculated that 12 per cent of all marriages represent Rh incompatibility, but only one of 15 such marriages results in erythroblastotic infants.

An important consideration in the prophylaxis of erythroblastosis is the determination of the Rh status of all women in the adolescent or childbearing age group, prior to any blood transfusion. By giving an Rh negative female Rh positive blood, sensitization is achieved, which increases the hazard of producing offspring with erythroblastosis fetalis. When a woman has been previously

sensitized by transfusion or intramuscular injection of blood, the disease is more apt to

positive fetus.

Once an erythroblastotic infant is born, however, treatment should be directed toward maintaining the hemoglobin at a satisfactory functional level until the hemolytic process subsides. This requires the use of blood transfusions. Current opinion is that group compatible, Rh negative blood should be used. Rh positive blood (especially the father's blood) is unsatisfactory because anti-Rh agglutinins from the mother which have not combined with its own erythrocytes are still circulating in the infant's blood stream, or are present in the infant's tissues. As a result additional blood destruction may take place, tissue reactions may occur and an increase in the severity of the disease results.

If group specific Rh negative blood is not available there are several alternatives. Group O, Rh negative blood with low titer of anti a and b iso-agglutinin may be used with safety. The use of the anti a and anti b Witebsky substance assures neutralization of the agglutinins in the serum of group O blood.

The use of maternal erythrocytes has been advocated for transfusion of the infant; the maternal serum being discarded because of the presence of Rh antibody. It was recommended that the cells be washed several times in sterile isotonic saline solution, then resuspended either in sterile isotonic saline or plasma from an individual of the same blood group as the mother. Study of the preservation of red cells has indicated, however, that such manipulation, particularly resuspension in saline, greatly attenuates the red cells so that their life span in the recipient is short. Furthermore, even five washings of the maternal erythrocytes fail to remove all of the Rh antibody and an appreciable amount is given to the recipient with the cells.

In addition, erythroblastotic infants often have low serum proteins so that the administration of serum, in addition to cells, is highly desirable.

In any event, it has become apparent that

as soon as a diagnosis of erythroblastosis has been made, blood transfusions should be given immediately. The illness may be considered to be a medical emergency, and the sooner therapy is instituted the better are the results. The blood must be given intravenously, not intramuscularly. If the mother gives a history of having had previous erythroblastotic babies, the disease may be anticipated even before the child is born, and under such circumstances a prophylactic transfusion can be given into the umbilical vein before the cord is cut and tied.

The recommended quantity of blood to be transfused is 10 cc per pound of body weight (Wiener and Weder). Thus, the average erythroblastotic infant will receive 75 cc of the proper blood intravenously as soon as possible after the diagnosis is made. It has been recommended that this be repeated the following day. In the average case, this

destroyed. This is sufficient to carry the infant over the period during which the Rh antibodies are being eliminated, and often for as long as a month the donor's erythrocytes are the only ones the infant possesses as shown by differential blood grouping tests.

Another, and probably better method of treatment has been described more recently (Wiener et al., Wallerstein, Diamond). Numerous names have been applied to this procedure, including exchange transfusion, replacement transfusion and exsanguination transfusion. Briefly stated, the procedure consists of bleeding and transfusing the infant simultaneously, or alternately bleeding and transfusing small amounts of the prop-

anemia. Death of the baby may result from a hemorrhagic diathesis which does not seem to be influenced by repeated blood transfusions. It has been postulated that adult blood might increase the danger of hemolysis in erythroblastic babies by activating an otherwise inactive Rh antibody. The more recent studies of the role of the liver and certain other tissues in the pathogenesis of erythroblastosis show that hemolysis should, if possible, be prevented. The replacement transfusion is designed to do this.

Replacement transfusion, if it is to be at all successful, must be carried out within 24 hours of the infant's birth. Ideally, an erythroblastotic baby should be anticipated, and the treatment performed immediately after birth. The treatment should take no longer than 60 to 90 minutes during which time, in the average sized infant, one blood volume or 250 cc of blood are removed, and 300 to 350 cc administered. With this procedure, only 25 per cent of the original Rh positive erythrocytes remain in the infant's circulation. If 400 cc of blood are removed, and 450 to 500 cc administered, 67 per cent of the infant's blood volume is replaced. If 900 cc of blood are removed and 1000 cc administered a replacement of about 88 per cent occurs. During the procedure two to four doses of 0.2 ml (2 mg) of heparin should be administered, the last dose midway through the transfusion so that little anticoagulant effect remains at its termination. The blood vessels most frequently used in carrying out the replacement are the radial artery or sagittal sinus for bleeding and saphenous vein for infusion, or the umbilical vein for either or both.

It must be borne in mind however, that exchange transfusions are associated with some risk and certain technical difficulties so that it is impractical for one who is untrained in the method to attempt it. Furthermore for its proper application, the physician must be prepared to carry out complete antepartum blood tests including Rh Hr blood typing of the parents, siblings, and at times other members of the family to determine the father's zygosity. Titration of the Rh antibody in the mother at intervals during pregnancy is also necessary in order to predict with any degree of certainty whether the fetus will be erythroblastotic. This again,

transfusion method the mortality rate remained relatively high. In addition, transfusions do not remove the agents responsible for the hemolysis in the infant but only supply the infant with functional erythrocytes to tide it over the period of severe anemia resulting from the hemolysis of its own cells. Further, the toxic products of hemolysis, either stromal or chemical, may be lethal to infants exhibiting only mild

involves technical procedures which necessitate training and experience

Often there arises the question of terminating the pregnancy in an Rh incompatible mating. Certainly, prematurity is an additional handicap to an erythroblastotic infant. However, if the father is known to be an Rh homozygous individual and the mother has had previous erythroblastotic babies, premature delivery should be seriously considered, especially if the maternal anti Rh iso antibody titer has risen sharply during the latter part of pregnancy. In such an event, replacement transfusion by a trained individual should be done immediately after delivery.

Finally some general considerations should be mentioned. An erythroblastotic baby should not be breast fed, for maternal colostrum and milk contain anti Rh iso antibodies. The hemorrhagic tendency exhibited by some of these infants is an indication of profound liver and endothelial damage resulting from anoxemia and the end products of hemolysis. As a result, therapy directed toward the prevention of hemolysis and anoxemia is the best approach, and this is accomplished most satisfactorily by the replacement transfusion. When hemorrhage does occur, however, the frequent administration of vitamin K, and the use of fresh blood for transfusion may be extremely valuable. After any transfusion or replacement transfusion therapy, two to four parenteral

use of oxygen, parenteral electrolytes glucose, and fluid may be of value as supportive measures depending on the complications which may arise during the infant's first days of life.

ROBERT W. HEINLE
MARTIN EPSTEIN

SPLENIC ANEMIA

The term splenic anemia has been abandoned by hematologists since the syndromes formerly included in this classification, have been reclassified more specifically on either physiologic or morphologic grounds. Congenital hemolytic anemia, sickle cell anemia and Cooley's anemia (see p 484) were for-

merly included in this group as were erythroblastosis fetalis (see p 485) and von Jaksch's anemia. The latter term is no longer used since it included various syndromes which have now been classified into one of the more clearly defined groups.

The conditions discussed here under the heading of splenic anemia are an unrelated group of diseases associated with anemia and splenomegaly, which is all that they have in common.

Primary splenic panhematopenia (Wise man and Doan) is a syndrome in which neutropenia is the outstanding feature, the experience of the writers. Varying degrees of anemia and thrombocytopenia are also present. Removal of the enlarged spleen is usually curative although relapses may occur.

Banti's syndrome is characterized by anemia, leukopenia, thrombocytopenia, splenomegaly, and cirrhosis of the spleen and liver. The clinical diagnosis is difficult to establish and it has been our experience that it is more often arrived at by ruling out other diseases capable of producing the clinical and laboratory findings. Splenectomy has been considered to be beneficial in some cases, with or without vascular anastomoses. In our cases such operative procedures have provided no benefit, possibly because the diagnosis was established too late. Vascular anastomoses have been followed by extensive and sometimes fatal thromboses.

The disease finally progresses to the stage of advanced cirrhosis. Esophageal varices may bleed profusely necessitating repeated blood transfusions. Ascites and edema are treated in the usual manner with paracentesis and diuretics as indicated.

Another group of diseases can be included under the heading of splenic anemias since, while the anemia is only one manifestation they enter into the differential diagnosis of any patient with anemia and splenomegaly. This is the group of lipid and nonlipid reticulo endothelioses including Gaucher's disease, Niemann-Pick disease, Hand-Christian-Schüller disease, and Letterer-Siwe disease. All of these may be associated with anemia, leukopenia, thrombocytopenia, and splenomegaly. In addition, hepatomegaly and lymphadenopathy may be present. There is no effective treatment for these diseases.

Splenectomy is even thought to accelerate the course of the disease in some instances although it may be justified in rare instances if the large spleen is causing mechanical difficulties. Blood transfusions should be given as dictated by the degree of the anemia. Radiation therapy (roentgen ray or radio active phosphorus) has produced temporary improvement in some cases but such improvement is slight and often absent.

ROBERT W HEINLE
MARTIN EPSTEIN

AGRANULOCYTOSIS

Agranulocytosis is usually seen following therapy with certain drugs in patients who probably have or have developed sensitivity to the drug in question. At this time thiouracil and to a lesser extent propyl thiouracil and related compounds are among the chief offenders. Any sulfonamide drug can probably induce the disease although sulfanilamide and sulfapyridine are much more likely to do so than sulfathiazole, sulfadiazine or sulfamerazine. Aminopyrine was a notoriously common cause of agranulocytosis until the danger was recognized and its widespread use was controlled. A variety of

sensitized individual

Clinically the various infections particularly ulcerative lesions of the oral mucous membranes which develop as a result of the severe neutropenia are the outstanding features of the disease. Furthermore it is now recognized that death results from the infections including pneumonia. If death from sepsis can be prevented the granulocytes eventually reappear in the bone marrow and blood and recovery is complete.

muscularly every 3 hours if the ordinary aqueous preparations are used or 300,000 units of one of the longer acting preparations at 24 hour intervals. Sulfadiazine or sulfamerazine may be similarly effective if it is certain that they were not concerned in the production of the disease in any given pa-

tient. Penicillin however is safer and fully as effective and should be used in preference to the sulfonamides.

Except for general symptomatic therapy other treatment than administration of penicillin is unnecessary and probably ineffective. The most widely used preparation has been pentanucleotide in intramuscular doses of 10 ml four times a day. After several years of observation however it is generally believed that this material produces little if any benefit in addition to which it is painful in the doses used and may produce undesirable systemic reactions.

Other materials which have been used in the treatment of agranulocytosis include extract of yellow bone marrow, other bone marrow extracts, liver extract, pteroylglutamic (folic) acid, various vitamins, blood transfusions and "stimulating" doses of roentgen rays. There is no satisfactory evidence that any of these are beneficial and the fact that so many different methods of treatment have been recommended is a reflection of the lack of utility of any one of them.

With the use of penicillin the mortality rate which in untreated cases exceeded 50 per cent has been reduced to almost nil. It appears evident that recovery will eventually occur if the patient is prevented from dying of sepsis in the meantime.

ROBERT W HEINLE
MARTIN EPSTEIN

REFERENCES

- Allen J G and Jacobson L M. Hyperheparinemia: Cause of Hemorrhagic Syndrome Associated with Total Body Exposure to Ionizing Rad. *Am J Science* 105:388 1947
- Allen J G et al. Some Observations on Bleeding Tendency in Thrombocytopenic Purpura. *Am J Med* 27:332 1947
- Berk L et al. Effectiveness of Vitamin B₁₂ in Combined System Disease: Rapid Regression of Neurologic Manifestations and Absence of Allergic Reactions in a Patient Sensitive to Injectable Liver Extracts. *New England J Med* 239:325 1948
- Dameshek W and Schwartz S M. Acute Hemolytic Anemia (Acquired Hemolytic Icterus: Acute Type). *Medicine* 19:231 1940
- Dahlborn I. Fetal Erythroblastosis. *JAMA* 12:633 1942
- Diamond L K. Replacement Transfusions as a Treatment for Erythroblastosis Fetalis. *Pediatrics* 25:90 1948

- Diamond, L. K. Medical Progress, Clinical Importance of Rh Blood Type *New England J Med*, 232 447, 475, 1945
- Diamond, L. K., Blackfan, K. D., and Baty, J. M. Erythroblastosis Fetalis and its Association with Universal Edema of Fetus, Icterus Gravis Neonatorum and Anemia of Newborn *J Pediat*, 1 269, 1932
- Doan, C. A., and Wright, C. H. Primary Congenital and Secondary Acquired Splenic Panhematopenia *Blood*, 1 10, 1946
- Elvehjem, C. A., Duckles, D., and Mendenhall, H. R. Iron vs Iron and Copper in Treatment of Anemia in Infants *Am J Dis Child*, 53 785, 1937
- Finland, M., et al. Cold Agglutinins, Cold Iso-
- and Iron on Hemoglobin Regeneration *J Lab & Clin Med*, 26 832 1941
- Heimle, R. W. and Welch, A. D. Folic Acid in Pernicious Anemia Failure to Prevent Neurologic Relapse *JAMA*, 133 739, 1947
- Hitzengerber, K. Die Rolle des Magens in der Blutbildung *Klin Wochenschr*, 13 1354 1934
- Israels, M. C. G. and Wilkinson, J. F. New Observations on Etiology and Prognosis of Achrestic Anemia *Quart J Med*, 9 163, 1940
- Israels, M. C. G., and Wilkinson, J. F. Achrestic Anemia *Quart J Med*, 5 69 1936
- Landsteiner, K. and Wiener, A. S. Agglutinable Factor in Human Blood Recognized by Immune Sera for Rhesus Blood *Proc Soc Exper Biol & Med*, 43 223 1940
- Levine, P. Pathogenesis of Erythroblastosis Fetalis, Review *J Pediat*, 23 656, Correction 24 221, 1944
- Levine, P., Katzin, E. M., and Burnham, L. Isoimmunization in Pregnancy, Its Possible Bearing on Etiology of Erythroblastosis Fetalis *JAMA* 116 825 1941
- Loutit, J. F., and Mollison, P. L. Hemolytic Icterus (Achloric Jaundice), Congenital and Acquired *J Path & Bact*, 58 711, 1946
- Lucke, H. Lower Nephron Nephrosis (Renal Lesions of Crush Syndrome, of Burns, Transfusions and Other Conditions Affecting Lower Segments of Nephrons) *Mil Surgeon*, 99 371, 1946
- Meyer, L. M. Folic Acid in Treatment of Pernicious Anemia *Blood* 2 50 1947
- Moore, C. V., et al. Activity of Synthetic Lactobacillus Casei Factor ("Folic Acid") as Antipernicious Anemia Substance Observations on 4 Patients 2 with Addisonian Pernicious Anemia, 1 with Nontropical Sprue and 1 with Pernicious Anemia of Pregnancy *J Lab & Clin Med*, 30 1056 1945
- Neary, E. H. Use of Molybdenized Ferrous Sulfate in Treatment of True Iron Deficiency Anemia of Pregnancy *Am J M Sc*, 212 76, 1946
- Ruckes, E. L., et al. Crystalline Vitamin B₁₂ *Science*, 107 396, 1948
- Ruckes, E. L., et al. Vitamin B₁₂, A Cobalt Complex *Science*, 108 134, 1948
- Seymour, W. B., Heimle, R. W., and Miller, F. H. Liver Dosage in Pernicious Anemia, Failure of Quantitative Storage of Hematopoietic Principle *New England J Med*, 225 675 1941
- Spies, T. D. *Experiences with Folic Acid* Chicago Year Book Publishers, 1947
- Spies, T. D. Effect of Folic Acid on Persons with Macrocytic Anemia in Relapse *JAMA*, 130 174 1946
- Stokstad, E. L. R., et al. Activity of Microbial Animal Protein Factor Concentrates in Pernicious Anemia *J Lab & Clin Med*, 33 860, 1948
- Strauss, M. B., and Castle, W. B. Parenteral Liver Therapy in Treatment of Pernicious Anemia *JAMA*, 98 1620, 1932
- Sturges, C. C., and Isaacs, H. Treatment of Pernicious Anemia with Desiccated Defatted Stomach *Am J M Sc*, 160 597, 1930
- Suarez, R. M., Spies, T. D., and Suarez, H. M., Jr. Use of Folic Acid in Sprue *Ann Int Med*, 26 643, 1947
- United States Pharmacopeia Anti Anemia Preparations Advisory Board. Report on Potency of Liver Products *JAMA*, 110 812, 1938
- Wallerstein, H. Substitution Transfusion New Treatment of Blood of Newborn Infant *Science* 103 583 1946
- West, R. Activity of Vitamin B₁₂ in Addisonian Pernicious Anemia *Science*, 107 398 1948
- Wiener, A. S., and Wexler, I. B. Use of Heparin when Performing Exchange Blood Transfusions in Newborn Infants *J Lab & Clin Med*, 31 1016 1946
- Wiener, A. S., and Wexler, I. B. Transfusion Therapy of Acute Hemolytic Anemia of Newborn *Am J Clin Path*, 13 393, 1943
- Wiener, A. S., Wexler, I. B., and Camm, E. Hemolytic Disease of Fetus and Newborn Infant, with Special Reference to Transfusion Therapy and Use of Biologic Test for Detecting Rh Sensitivity *Am J Dis Child*, 68 317, 1944
- Wiener, A. S., Wexler, I. B., and Shulman, A. Therapy of Severe Erythroblastosis Fetalis with Repeated and Massive Exchange Transfusions *Am J Clin Path*, 18 141, 1943
- Wilkinson, J. F. Folic Acid *Brit M J*, 1 771, 822 1948
- Wilkinson, J. F. Diseases Associated with Pernicious Anemia in Study of 370 Cases *Quart J Med*, 2 281, 1933
- Wiseman, B. K., and Doan, C. A. A Newly Recognized Granulopenic Syndrome Caused by Excessive Splenic Leukolysis and Successfully Treated by Splenectomy *Ann Int Med*, 30 776 1945
- Witelsky, E., Anderson, G. W., and Heide, A. Demonstration of Rh Antibody in Breast Milk *Proc Soc Exper Biol & Med*, 49 179, 1942
- Witelsky, E., Rubin, M. I., and Blum, L. Studies in Erythroblastosis Fetalis Activation of Incomplete Rh Antibody by Blood Serum of Full Term

and Premature Newborn Infants *J Lab & Clin Med* 32 1330 1945
 Zuelzer W W and Ogden F N Folic Acid Therapy in Macrocytic Anemias of Infancy *Proc Soc Exper Biol & Med* 61 176 1946

INFECTIOUS MONONUCLEOSIS

Fortunately infectious mononucleosis is a benign self limited disease as there is no specific treatment. The acute phase usually runs its course in about 2 weeks time. The lingering asthenia which follows however may be most distressing and last for several weeks or months.

Since associated Vincent's infection often occurs a saturated solution of sodium perborate or half strength solution of hydrogen peroxide may be useful for cleansing the mouth and throat. Penicillin 30 000 units every 3 hours is of value if hemolytic streptococci are found as secondary invaders.

none is perhaps quite as important as rest during the active phase of the illness. As with infectious hepatitis recrudescence of the disease is likely to occur if too early ambulation or return to full activity is attempted.

Convalescent blood or serum has been recommended as of value but these substances usually can be obtained only at the height of an epidemic.

Opinion varies as to how strict the isolation of these patients should be. During epidemics in susceptible communities reasonable precautions should be taken with excreta utensils and patient contacts for approximately 2 weeks. In sporadic cases no special precautions are needed. When death intervenes as it occasionally does it is usually due to some complication such as spontaneous rupture of the spleen. When splenic rupture occurs immediate surgical intervention is mandatory.

Death also has resulted from respiratory paralysis associated with a Guillain Barré syndrome, edema of the glottis and supervening infection.

Thrombocytopenic purpura occasionally occurs as a complication of infectious mononucleosis. In most instances it disappears spontaneously during convalescence. How-

ever in one instance splenectomy was successfully performed.

Hepatitis which frequently occurs with infectious mononucleosis must be treated with prolonged bed rest until the liver function returns to normal. In all cases of mononucleosis the liver function should be studied.

EDWIN D BAYRO

REFERENCE

Contratto A W Infectious Mononucleosis: Study of 196 Cases *Arch Int Med* 73 449 1944

THE LEUKEMIAS

Acute Leukemia Acute leukemia a disease of unknown etiology progresses rapidly with few exceptions to a fatal termination. No cure is known. In the past treatment has been entirely palliative. General supportive measures and transfusions have been the mainstay of treatment. Irradiation in most cases is contraindicated but in exceptional cases in which leukemic tumors are encroaching on or interfering with the function of vital organs roentgen therapy in light dosage may be given. The administration of radioisotopes such as radiophosphorus is largely ineffectual although some investigators have maintained that the survival times of patients can sometimes be slightly prolonged with this form of treatment.

While a cure for acute leukemia remains unknown hope that the disease eventually might be controlled has been kindled recently by the work of Farber and his associates. Farber observed that the leukemic process was intensified or accelerated in children who were treated with pteroylglutamic acid (folic acid). He suggested that chemical compounds which were biologically antagonistic to pteroylglutamic acid might inhibit the leukemic process. Several so-called antagonists to folic acid have been studied; the most effective of which appear to be aminopterin (4 aminopteroylglutamic acid), amethopterin (4 aminomethylpteroylglutamic acid) and amino-anfol (4 aminopteroylaspatic acid). Impressive remissions have been obtained with these substances the incidence of remissions being greater in children than in adults.

The mode of action of the antagonists to folic acid in leukemia is not as yet known. Normal as well as leukemic tissues are affected but the growth of young rapidly growing cells is impaired more seriously than that of more mature slowly growing cells.

The administration of antagonists of folic acid to patients having acute leukemia is followed in most cases by a gradual or rapid reduction in the leukocyte count and a diminution in the number of immature leukemic cells in both the blood and the bone marrow. Weakness, often profound soreness of the tongue or mucous membranes of the mouth and throat, not infrequently followed by ulceration, diarrhea and excessive loss of hair may develop any time during the first few weeks of therapy. Remissions which may be partial or complete occur most frequently after a month or more of treatment.

Antagonists of folic acid are administered intramuscularly. Recommended daily doses are as follows:

Dose	Children	Adults
Aminopterin	0.5 to 1.0 mg	0.5 to 2.0 mg
Amethopterin	3.0 to 5.0 mg	5.0 to 10.0 mg
Amino an fol	25.0 to 50.0 mg	25.0 to 75.0 mg

The size of the individual dose should be gauged by the age, weight and physical condition of the patient. Since the range between a therapeutic and a toxic dose is negligible, it is usually necessary to induce toxic manifestations in order to obtain the desired clinical result. However, if ulcerative stomatitis, diarrhea, acute bleeding or an unusually rapid fall in the leukocyte count occurs, the administration of antagonists of folic acid immediately should be stopped until the cause of the complication has been determined. If complications do not develop, treatment may be carried on without interruption for weeks or months. During remissions the administration of antagonists may be continued in slightly smaller doses than before.

All of the antagonists of folic acid studied are toxic. The most important toxic manifestations are stomatitis, diarrhea, ulcerative lesions at any site in or throughout the gastrointestinal tract, gastrointestinal hemorrhage which may be massive and severe

hypoplasia or aplasia of the bone marrow. Toxic manifestations cannot be reversed readily by the administration of pteroylglutamic (folic) acid or liver extract. The most effective remedy is the immediate withdrawal of the drug for 4 to 7 or more days.

Information concerning the incidence and duration of remissions is as yet incomplete. Stickney Mills and their associates at the Mayo Clinic have treated 21 children and 33 adults. Among the children, 10 had remissions; those of 5 were fairly complete. These lasted from 1½ to 4 months. Eighteen of the 21 children now are dead. Among the adults, the incidence of remissions was only approximately 18 per cent. The duration of remissions, however, was similar to that observed in children.

Some evidence suggests that acute lymphocytic leukemia responds more favorably to treatment with antagonists of folic acid than acute granulocytic or acute monocytic leukemia does. Recently Doan and his associates have suggested that ethyl carbamate (urethane) be employed in the treatment of acute granulocytic leukemia and nitrogen mustard in the treatment of acute monocytic leukemia. They reserved the antagonists of folic acid for acute lymphocytic leukemia. This matter, however, requires further study before a final decision can be made.

Chronic Leukemia **CHRONIC GRANULOCYTIC LEUKEMIA** While the average duration of life of patients having either chronic granulocytic or chronic lymphocytic leukemia is approximately 3 years, there is marked variation in individual cases and patients are known to have lived 15 years or longer. There are as yet no conclusive statistical data that treatment by any of the methods available at present significantly prolongs the lives of leukemic patients. However, treatment during the earlier stages of the disease almost always alleviates distressing symptoms and in cases in which essentially complete remissions can be induced, there may be a return to a sense of normal well-being, thus permitting these patients to lead normal and useful lives. In the later stages the disease is more difficult to control and eventually death occurs despite treatment.

Röntgen Therapy Röntgen rays have been used in the treatment of leukemia since early in this century. Many different tech-

nics have been described which utilize low or high voltage local irradiation over the spleen lymph nodes viscera with leukemic infiltrations or localized leukemic tumors irradiation of the bones or of the whole body. The choice of technic depends largely on the facilities available to the roentgen therapist. Since treatment with low voltage to the spleen induces remissions in most cases it has been the practice at the Mayo Clinic to administer the smallest effective dose in the shortest possible time thereby

rays

The indications for treatment are a rapidly rising leukocyte count or an increase in immature forms the development or presence of anemia pressure symptoms progressive loss of weight evidence of leukemic infiltration of vital organs and pain resulting from leukemic invasion. Unless unduly high an increased leukocyte count alone is not an indication for treatment. Leukemic patients with leukocyte counts in the neighborhood of 100 000 cells per cubic millimeter or more may show no signs of progression of the disease for months or even, occasionally for longer periods.

Roentgen irradiation may be given daily or at less frequent intervals. If a daily schedule is being utilized leukocyte counts should be made each morning before the patient is treated. Treatment should be stopped altogether or interrupted temporarily if the leukocyte count falls rapidly if irradiation sickness becomes severe and dehydration develops as a result of frequent vomiting if the condition of the patient suddenly becomes worse or if complications such as severe bleeding occur. If treatment does not have to be interrupted for one of the above reasons it is continued until the desired result is obtained that is until marked diminution in the leukocyte count with reduction in the size of the spleen or lymph nodes or both occurs.

No specific rules can be made as to just when treatment should be discontinued but it should be remembered that a significant drop in the leukocyte count occurs during the first 2 to 3 weeks after cessation of therapy. For example, if the leukocyte count

has fallen slowly and treatment is terminated when the count approaches 30 000 cells per cubic millimeter of blood a drop to 10 000 cells or even less not infrequently occurs after treatment is stopped. On the other hand in cases in which the fall in leukocytes is rapid the continued administration of roentgen therapy until the leukocyte count has reached 30 000 cells per cubic millimeter would be extremely hazardous because an extreme degree of leukopenia might be induced. In such instances it is advisable to terminate treatment when the leukocyte count has fallen to 60 000 or 75 000 cells per cubic millimeter.

Individuals with markedly elevated counts but when necessary it may be carried out safely if proper precautions are taken and the patient is watched carefully. However,

myelosclerosis (agranulocytic myeloid metaplasia), which may simulate closely leukopenic myelogenous leukemia.

During periods of remission patients should be followed carefully. The remission may last from a few weeks to many months. Recurrence of symptoms progressive increase in the leukocyte count an increase in the number of immature forms in the blood and development of anemia or an increase

tered is an effective and valuable means for controlling this disease for long periods. Eventually however refractoriness to irradiation develops. Some of the patients may respond temporarily at least to other forms of therapy such as the administration of urethane. In a fairly high proportion of cases acute leukemia develops as a terminal event. Treatment with roentgen rays at this stage of the disease is ineffectual.

The principal disadvantages of roentgen therapy are (1) irradiation sickness (2) the time required for treatment, and (3) the cost of repeated courses of therapy. There is some evidence to suggest that irradiation sickness may be prevented or mitigated.

fairly high proportion of cases by the intravenous injection of 100 to 200 mg of pyridoxine hydrochloride a half hour before roentgen treatment is administered (Wells and Popp). Recently, dramamine (B dime thylamino ethylbenzohydryl ether 8 chloro theophyllinate) 50 mg three times daily, also has been found to be beneficial (Beeler et al). Proper ventilation of rooms when treatment is given, lengthening of the interval between treatments for patients who have had irradiation previously, and the administration of a sedative, such as a barbiturate, an hour or two before treatment are also helpful. If irradiation sickness accompanied by frequent vomiting develops despite these precautions, dehydration should be prevented by parenteral administration of fluids. The intravenous administration of solutions of glucose is particularly helpful.

Radium Radium has been used successfully in the treatment of chronic leukemia but it does not appear to have any particular advantage over roentgen irradiation. The mode of action, the indications and contraindications and the measures utilized to prevent overtreatment are essentially the same.

Since then, this form of therapy has been used extensively at a number of institutions in this country. Ample data concerning the immediate results of administration of the isotope have been reported but information concerning the long range effects is incomplete. Recently, however, Lawrence and his co-workers have presented evidence indicating that the comfortable life of leukemic patients treated with radioactive phosphorus is prolonged.

The radioactive phosphorus originally used by Lawrence and others was prepared by bombarding ordinary red phosphorus (P^{31}) with deuterons in the cyclotron. At present, radiophosphorus is made from neutron bombardment of sulfur in the atomic pile. The radiophosphorus in both cases is the same. Carrier free radiophosphorus, brought to isotonicity by the addition of solution of sodium chloride, is now available in which essentially all of the phosphate present is radioactive. The beta ray activity

of the solution is standardized in terms of microcurie radium equivalents against a uranium beta ray standard. Following sterilization, this solution can be administered intravenously or given orally.

The half life, absorption, excretion and distribution of radioactive phosphorus are discussed in the section dealing with the treatment of polycythemia vera. Calculation of dosage is based on equivalent roentgens of whole body radiation delivered by the quantity of radioactive phosphorus administered. The formulas devised by Tobias facilitate the conversion of doses of radioactive phosphorus in millicuries to roentgen equivalents. For intravenous administration the total dose in roentgen equivalent physical* is

$$N \times T \times 1.44 \times 0.52 \times \frac{40}{\text{weight in grams}}$$

where N represents microcuries, T signifies half life, the figure 1.44 is an expression obtained from the integration of the dose over infinite time, the factor 0.52 relates to the rate of absorption and excretion, and the figure 40 is the initial dose rate (derived from the fact that 1 millicurie of radioactive phosphorus per gram of tissue will give 40 roentgens of irradiation in a period of 24 hours). For oral administration, the formula is the same except for a change in the factor relating to rate of absorption and excretion. This now becomes 0.38.

In order to afford prolonged and fairly constant irradiation of leukemic tissues radioactive phosphorus is administered either intravenously or orally, once or twice a week until the desired effect is obtained. Thus, the method of administration differs from that employed in the treatment of polycythemia vera. As a general rule, initial doses of from 1 to 3 mc are given. Thereafter, smaller amounts, usually from 0.5 to 1.5 mc are administered, the size of the individual dose depending in part on frequency of administration and in part on the hematopoietic and clinical response obtained. As the leukocyte count diminishes, it is advisable gradually to reduce each dose of radioactive phosphorus. Since there is considerable individual variation in the response

* One roentgen equivalent physical (rep) is the dose of ionizing radiation which will deliver 83 ergs per gram.

of patients to this form of therapy no hard and fast rules can be given. However careful hematologic observation is essential. Leukocyte, erythrocyte and platelet counts should be obtained before each injection of the isotope.

The total quantity of radioactive phosphorus required to induce remissions is extremely variable. In some cases 40 or 50 mc administered intravenously over a period of 1 or 2 weeks may be sufficient to produce the desired result; in others total doses of 25 or 30 mc given over periods of many weeks may be required.

Treatment with radioactive phosphorus

is accompanied by diminution in the size of the spleen and lymph nodes occurs. The leukocyte count gradually falls and the number of immature cells in the peripheral blood is reduced. Concomitantly if anemia is present prior to treatment there is a gradual increase in the erythrocyte count, not infrequently to a normal value.

The duration of remissions is variable, lasting from a few months to more than a year. When relapse occurs remissions can again be induced by giving additional courses.

The principal advantages of treatment with radioactive phosphorus appear to be the ease with which generalized irradiation

can be achieved and the fact that the incidence of an acute leukemic phase as a terminal event is higher than in patients treated solely by means of roentgen irradiation. The latter, however, appears to be offset by the fact that a comfortable and useful life is probably longer than among patients treated with roentgen rays.

Urethane (Ethyl Carbamate) Urethane was introduced as a therapeutic agent for leukemia by Paterson Haddow and Ap Thomas and Watkinson in 1946. The administration of this agent in selected cases produces a fall in the leukocyte count, reduction in the number of immature forms in the blood stream, diminution in the size of the spleen and symptomatic improvement. As the leuko-

cyte count falls the erythrocyte count and values for hemoglobin if below normal prior to treatment frequently increase and in many cases return to normal.

Although urethane may be administered intramuscularly or intravenously it is most easily given by mouth. Moreover the intravenous route is not without danger. Paterson and associates originally prescribed urethane in a solution of chloroform and syrup of orange, but this mixture no longer is utilized because of the possible deleterious effects of chloroform. Gelatin capsules containing 0.5 gm or 0.3 gm and 0.5 gm enteric coated capsules or tablets as well as a solution in the form of an elixir now are available for

administration. The most common and pleasant side effects such as anorexia, nausea and vomiting. Experience has shown that as small a dose as will produce a gradual reduction in the leukocyte count is most satisfactory, although a month or more may be required to produce the desired clinical results. As the leukocyte count falls the daily dose of urethane should be diminished. This necessitates blood examinations twice or thrice a week until the leukocyte count approaches normal levels. Once values approximating normal have been reached the patient should be placed on maintenance doses of from 0.5 to 1.5 gm daily. If administration of the drug is stopped the leukocyte count increases rapidly and clinical manifestations of relapse develop. During periods of maintenance therapy examinations of blood should be performed every week or two because adjustments in dosage not infrequently have to be made. Since urethane does not have a cumulative action it may be administered continuously for long periods.

Intolerance to the drug has been reported. However complications of this type appear to be rare.

Symptoms of intolerance to the drug are anorexia, nausea, vomiting and drowsiness. These symptoms are encountered infrequently in patients receiving moderate doses of urethane but they are common in those

receiving larger doses (30 to 50 gm daily) If sufficiently distressing the administration of urethane should be discontinued and some other form of therapy instituted

Nitrogen Mustards These compounds have been used principally for the treatment of the malignant lymphomas. However they have been studied rather extensively for their potential value as therapeutic agents in leukemia as well. The comprehensive report of Burchenal and associates showed that methyl bis (β chloroethyl) amine and *tris* (β chloroethyl) amine produced results in chronic granulocytic leukemia similar to those obtained with roentgen irradiation or with radioactive phosphorus. As a rule however the remissions were somewhat shorter than those noted after irradiation. In chronic lymphocytic leukemia the response to treatment was satisfactory among patients in an early stage of the disease but poor among patients with far advanced disease. In acute leukemia treatment with nitrogen mustard proved to be of little value although temporary symptomatic relief was observed in some cases.

The pharmacology, mode of action, method of administration, dosage of the nitrogen mustards and the complications arising from this form of therapy are discussed in the section on Hodgkin's disease and allied disorders.

so
U
disuse after the introduction of roentgen irradiation until the work of Forkner and Scott in 1931 revived interest in it. Bene
The
att is
as follows: Five minims (0.3 cc) diluted in fruit juice are administered with or immediately after meals three times daily for 2 or 3 days. Then the dose is increased by 3 minims daily (to 8 minims three times a day) then to 7 minims three times a day and so on until 10 minims three times a day are being given. Thereafter the dose is increased by 1 minim daily until the desired effect is obtained or until symptoms of toxemia develop. In either event treatment is suspended for 2 to 5 days then resumed by reducing the dose from the maximum by 1 minim daily

until a maintenance dosage of 5 to 8 minims three times a day is attained. Maintenance therapy may be continued for long periods but adjustments in dosage may be required from time to time.

Toxic manifestations frequently occur. These include anorexia, nausea, vomiting, restlessness, insomnia, loss of weight, diarrhea and with prolonged treatment pigmentation and keratosis of the skin and peripheral neuritis. Because of the toxicity of the drug, roentgen irradiation, radioactive phosphorus or urethane therapy is to be preferred. However the administration of Fowler's solution to patients who have become refractory to roentgen treatment sometimes results in temporary improvement and may therefore be worth a trial.

Other Agents: Benzene at one time was widely advocated as a useful agent for treating chronic granulocytic leukemia. Initial doses of 30 gm daily were recommended, the daily dose gradually being increased to 40 or 50 gm. The drug then was withdrawn gradually as the leukocyte count fell. This method now is rarely employed in this country.

Other methods of treatment such as the administration of various organ extracts (spleen), antimony and aminopyrine have not proved to be of value.

Splenectomy This procedure is contraindicated except in rare instances in which hemolytic anemia is superimposed on the basic leukemic process. In such cases splenectomy may be followed by a lessening of or cessation of excessive hemolysis and thus the patient's life may be prolonged.

General Measures There is little or no need to restrict the activities of leukemic patients during periods of remission. However during periods of relapse some restriction is advisable. Rest in bed is desirable in patients with fever or far advanced leukemia with an associated severe anemia.

A well balanced, nutritious, isocaloric diet will meet the requirements of most patients. Over a high
even meals
increased

basal metabolic rate or with fever.

Severe infections are particularly likely to develop in cases of leukemia, especially in the late stages of the disease or in those in

which leukopenia is present. Ulcerative lesions in the mouth or throat not infrequently occur and may be followed by the development of bacteremia. Oral hygiene therefore is important. Thorough cleansing of the mouth after each meal with an alkaline mouth wash or a mild antiseptic solution such as hydrogen peroxide is desirable and a soft toothbrush should be used for brushing the teeth in order to minimize the risk of injuring the mucous membranes. In the presence of serious infections antibiotic agents or the sulfonamides or both are especially useful. For ulcerations of the skin resulting from necrosis of localized leukemic tumors the local application of sulfathiazole powder will effectively control secondary infection in the ulcerated area in most cases and not infrequently will be followed by healing.

Treatment of the anemia associated with chronic leukemia may present a difficult problem for the physician if the anemia persists after the leukocyte count has been reduced by roentgen irradiation or other measures. In such cases the persistence of anemia implies the existence of far advanced disease and the administration of iron extracts of liver, folic acid or vitamin B₁₂ is ineffectual. The judicious use of properly spaced transfusions of blood is beneficial although the benefit derived from this procedure is only temporary. Sturges advocated the use of fresh blood for patients with thrombocytopenia or ulcerative lesions of the mucous membranes but preserved or bank blood is satisfactory for use in cases in which these complications do not occur.

CHRONIC LYMPHOCYTIC LEUKEMIA. *Roentgen Irradiation.* This method of treatment remains the treatment of choice for chronic lymphocytic leukemia. Remissions often of long duration can be induced with it and with repeated courses of treatment the disease may be controlled and a comfortable life afforded for several years. The indications for treatment are (1) marked adenopathy of the peripheral lymph nodes (2) pressure symptoms resulting from enlargement of mediastinal or intra abdominal lymph nodes from an enormously enlarged spleen or from localized leukemic growths in vital areas and (3) a high leukocyte count with an associated anemia. On the

other hand if there is no significant adenopathy enlargement of the spleen or anemia it is usually advisable to withhold treatment until one or more of these manifestations de-

velop. Chronic lymphocytic leukemia may live for years before adenopathy, splenomegaly or anemia becomes manifest.

Radioactive phosphorus. In general roentgen irradiation is to be preferred to treatment with radioactive phosphorus in chronic lymphocytic leukemia for two reasons. (1) Roentgen therapy affords maximal irradiation of lymphoid tissue with only a relatively minor inhibitory effect on hematopoiesis in the bone marrow. (2) the administration of radioactive phosphorus results in greater irradiation of the marrow than of lymphoid tissue where maximal irradiation actually is desired. Consequently the incidence of thrombocytopenia and anemia is higher among patients treated with radioactive phosphorus than among those receiving roentgen irradiation. The principal indication for treatment with radioactive phosphorus in chronic lymphocytic leukemia is evidence of massive leukemic involvement of the bone marrow on sternal aspiration together with associated anemia. In cases of this type administration of the isotope not infrequently induces remissions and results in improvement of the anemia. The dosage and method of administration are similar to those employed in chronic granulocytic leukemia.

Urethane. The results of the administration of urethane to patients having chronic lymphocytic leukemia are more variable than those obtained in chronic granulocytic leukemia. In cases in which the response is favorable the leukocyte count falls to values approaching normal, the differential count approaches a more normal pattern, diminution in the size of enlarged lymph nodes and spleen occurs and values for hemoglobin and erythrocytes frequently rise. In general however roentgen irradiation produces more uniformly good results and therefore is to be preferred to urethane.

Nitrogen Mustards. See discussion in section on Hodgkin's Disease and Allied Disorders.

receiving larger doses (30 to 50 gm daily) If sufficiently distressing, the administration of urethane should be discontinued, and some other form of therapy instituted

Nitrogen Mustards These compounds have been used principally for the treatment of the malignant lymphomas. However, they have been studied rather extensively for their potential value as therapeutic agents in leukemia as well. The comprehensive report of Burchenal and associates showed that methyl bis (β chloroethyl) amine and tris (β chloroethyl) amine produced results in chronic granulocytic leukemia similar to those obtained with roentgen irradiation or with radioactive phosphorus. As a rule, however, the remissions were somewhat shorter than those noted after irradiation. In chronic lymphocytic leukemia the response to treatment was satisfactory among patients in an early stage of the disease but poor among patients with far advanced disease. In acute leukemia treatment with nitrogen mustard proved to be of little value, although temporary symptomatic relief was observed in some cases.

The pharmacology, mode of action, method of administration, dosage of the ni

hed disorders

Arsenicals Arsenic in the form of Fowler's solution (solution of potassium arsenite U.S.P.), first used as early as 1865 fell into disuse after the introduction of roentgen irradiation until the work of Forkner and Scott in 1931 revived interest in it. Beneficial results can be obtained with it in some cases, but it is more toxic than urethane. The method described by Forkner and Scott is as follows: Five minims (0.3 cc) diluted in fruit juice are administered with or immediately after meals three times daily for 2 or 3 days. Then the dose is increased by 3 minims daily (to 6 minims three times a day, then to 7 minims three times a day and so on) until 10 minims three times a day are being given. Thereafter, the dose is increased by 1 minim daily until the desired effect is obtained or until symptoms of toxemia develop. In either event, treatment is suspended for 2 to 5 days then resumed by reducing the dose from the maximum by 1 minim daily

until a maintenance dosage of 5 to 8 minims three times a day is attained. Maintenance therapy may be continued for long periods but adjustments in dosage may be required from time to time.

Toxic manifestations frequently occur. These include anorexia, nausea, vomiting, restlessness, insomnia, loss of weight, diarrhea, and with prolonged treatment, pigmentation and keratosis of the skin and peripheral neuritis. Because of the toxicity of the drug, roentgen irradiation, radioactive phosphorus, or urethane therapy is to be preferred. However, the administration of Fowler's solution to patients who have become refractory to roentgen treatment some times results in temporary improvement and may, therefore, be worth a trial.

Other Agents Benzene at one time was widely advocated as a useful agent for treating chronic granulocytic leukemia. Initial doses of 30 gm daily were recommended, the daily dose gradually being increased to 40 or 50 gm. The drug then was withdrawn gradually as the leukocyte count fell. This method now is rarely employed in this country.

Other methods of treatment, such as the administration of various organ extracts (spleen), antimony, and aminopyrine have not proved to be of value.

Splenectomy This procedure is contraindicated except in rare instances in which hemolytic anemia is superimposed on the basic leukemic process. In such cases, splenectomy may be followed by a lessening of or cessation of excessive hemolysis and thus the patient's life may be prolonged.

General Measures There is little or no need to restrict the activities of leukemic patients during periods of remission. However, during periods of relapse some restriction is advisable. Rest in bed is desirable in patients with fever or far advanced leukemia with an associated severe anemia.

A well balanced, nutritious, isocaloric diet will meet the requirements of most patients during periods of remission. However, a high caloric diet with nourishment between meals is advisable for patients with an increased basal metabolic rate or with fever.

Severe infections are particularly likely to develop in cases of leukemia, especially in the late stages of the disease or in those in

which leukopenia is present. Ulcerative lesions in the mouth or throat not infrequently occur and may be followed by the development of bacteremia. Oral hygiene therefore is important. Thorough cleansing of the mouth after each meal with an alkaline mouth wash or a mild antiseptic solution such as hydrogen peroxide is desirable and a soft toothbrush should be used for brushing the teeth in order to minimize the risk of injuring the mucous membranes. In the presence of serious infections antibiotic agents or the sulfonamides or both are especially useful. For ulcerations of the skin resulting from necrosis of localized leukemic tumors the local application of sulfathiazole powder will effectively control secondary infection in the ulcerated area in most cases and not infrequently will be followed by healing.

Treatment of the anemia associated with chronic leukemia may present a difficult problem for the physician if the anemia persists after the leukocyte count has been reduced by roentgen irradiation or other measures. In such cases the persistence of anemia implies the existence of far advanced disease and the administration of iron extracts of liver, folic acid or vitamin B is ineffectual. The judicious use of properly spaced transfusions of blood is beneficial although the benefit derived from this procedure is only temporary. Sturgis advocated the use of fresh blood for patients with thrombocytopenia or ulcerative lesions of the mucous membranes but preserved or bank blood is satisfactory for use in cases in which these complications do not occur.

CHRONIC LYMPHOCYTIC LEUKEMIA. *Roentgen Irradiation.* This method of treatment remains the treatment of choice for chronic lymphocytic leukemia. Remissions often of long duration can be induced with it and with repeated courses of treatment the disease may be controlled and a comfortable life afforded for several years. The indications for treatment are (1) marked adenopathy of the peripheral lymph nodes, (2) pressure symptoms resulting from enlargement of mediastinal or intra-abdominal lymph nodes from an enormously enlarged spleen or from localized leukemic growths in vital areas and (3) a high leukocyte count with an associated anemia. On the

other hand if there is no significant adenopathy, enlargement of the spleen or anemia it is usually advisable to withhold treatment until one or more of these manifestations develop even though the leukocyte count may be in the neighborhood of 100,000 cells per cubic millimeter. Some patients who have chronic lymphocytic leukemia may live for years before adenopathy, splenomegaly or anemia becomes manifest.

Radiophosphorus. In general roentgen irradiation is to be preferred to treatment with radioactive phosphorus in chronic lymphocytic leukemia for two reasons: (1) Roentgen therapy affords maximal irradiation of lymphoid tissue with only a relatively minor inhibitory effect on hematopoiesis in the bone marrow; (2) the administration of radioactive phosphorus results in greater irradiation of the marrow than of lymphoid tissue where maximal irradiation actually is desired. Consequently the incidence of thrombocytopenia and anemia is higher among patients treated with radioactive phosphorus than among those receiving roentgen irradiation. The principal indication for treatment with radioactive phosphorus in chronic lymphocytic leukemia is evidence of massive leukemic involvement of the bone marrow on sternal aspiration together with associated anemia. In cases of this type administration of the isotope not infrequently induces remissions and results in improvement of the anemia. The dosage and method of administration are similar to those employed in chronic granulocytic leukemia.

Urethane. The results of the administration of urethane to patients having chronic lymphocytic leukemia are more variable than those obtained in chronic granulocytic leukemia. In cases in which the response is favorable the leukocyte count falls to values approaching normal, the differential count approaches a more normal pattern, diminution in the size of enlarged lymph nodes and spleen occurs and values for hemoglobin and erythrocytes frequently rise. In general however roentgen irradiation produces more uniformly good results and therefore is to be preferred to urethane.

Nitrogen Mustards. See discussion in section on Hodgkin's Disease and Allied Disorders.

General Measures These are essentially the same as those outlined for chronic granulocytic leukemia

CHRONIC LEUKEMIC RETICULO ENDOTHELIOSIS This disease is not infrequently consistent with a comparatively long life, some patients living for 10 years or more. In our experience, roentgen irradiation and properly spaced blood transfusions give the best results. However, roentgen irradiation should be administered in courses as sparingly as possible, and only if pressure symptoms from an enormously enlarged spleen become especially troublesome or if the leukocyte count is unduly high. Anemia is not an indication for the administration of roentgen therapy. Treatment with radioactive phosphorus or the nitrogen mustards is contra-indicated because of the risk of seriously inhibiting hematopoiesis, resulting in the development or intensification of leukopenia, anemia, and thrombocytopenia. Thrombocytopenia is a particularly serious complication because of the danger of fatal hemorrhage.

BYRON E. HALL

REFERENCES

- Beeler, J. W., Tillisch, J. H., and Popp, W. C. New Drug in Treatment of Radiation Sickness. *Proc Staff Meet, Mayo Clin.*, 24:477, 1949.
- Burchenal, J. H., et al. The Nitrogen Mustards in the Treatment of Leukemia. *Cancer* 2:1, 1949.
- Farber, S. Some Observations on the Effect of Folic Acid Antagonists on Acute Leukemia and Other Forms of Incurable Cancer. *Blood*, 4:160, 1949.
- Farber, S. Temporary Remissions in Acute Leukemia Produced by Folic Acid and Antagonists. *Proc Dig Laboratories & Research, Children's Medical Center, Boston* 1:1, 1948.
- Farber, S. et al. Temporary Remissions in Acute Leukemia in Children Produced by Folic Acid Antagonist 4-Aminopteroyl Glutamic Acid (Aminopterin). *New England J Med*, 238:787, 1948.
- Forkner, C. E., and Scott, T. F. M. Arsenic as Therapeutic Agent in Chronic Myelogenous Leukemia, Preliminary Report. *JAMA*, 97:3, 1931.
- Hall, H. E. Therapeutic Use of Radioactive Phosphorus in Polycythemia Vera, Leukemia, and Allied Diseases in *Symposium on the Use of Isotopes in Biology and Medicine*. Madison: University of Wisconsin Press, 1948.
- Lawrence, J. H., et al. Chronic Myelogenous Leukemia, Study of 129 Cases in Which Treatment
- Was with Radioactive Phosphorus. *JAMA*, 136:672, 1948.
- Lumazar, L. R. Leukemia, Lymphoblastoma, and Polycythemia Vera. *Minnesota Med*, 32:892, 1949.
- Paterson, E., et al. Leukemia Treated with Urethane Compared with Deep X-ray Therapy. *Lancet*, 1:677, 1946.
- Stuckney, J. M., et al. Treatment of Acute Leukemia with Folic Acid Antagonists. *Proc Staff Meet, Mayo Clin*, 24:525, 1949.
- Stroebel, C. F., and Hall, H. E. Unpublished Data.
- Sturges, C. C. *Hematology*. Springfield, Ill: C. C. Thomas, 1948.
- Tobias, C. A. The Standardization of the Measurement of Radioactive Phosphorus. Unpublished Data.
- Webster, J. J. Urethane in Leukemia. *JAMA* 135:901, 1947.
- Wells, J. J., and Popp, W. C. Use of Pyridoxine Hydrochloride in Treatment of Radiation Sickness, Preliminary Report. *Proc Staff Meet, Mayo Clin*, 22:482, 1947.

HODGKIN'S DISEASE AND ALLIED DISORDERS

The classification of this group of diseases has been a controversial subject for many years. None of the proposed classifications have found universal acceptance. However, despite certain shortcomings, we have found the classification made by Jackson and Parker particularly useful. Fortunately, from the standpoint of therapy, the entire group may be considered together. This discussion, therefore, will embrace the treatment of Hodgkin's disease, lymphosarcoma, lymphocytoma, lymphoblastoma (used in the strict sense), reticulum cell sarcoma, and giant follicle lymphoma (giant follicular hyperplasia).

While it is generally conceded that active treatment affords a more comfortable life, few statistics are available concerning survival rates in treated and untreated groups of patients. Stout's report, therefore, is significant. Survival rates are presented from a study of 119 treated and 51 untreated patients with lymphosarcoma. Five years after the diagnosis was made 23.5 per cent of the treated group survived, and 15 per cent were symptom free, whereas only 2 per cent of the untreated group survived and none

free of symptoms, whereas none of the un-

treated group were alive. Thus, it would appear that active treatment does prolong life, at least in cases of lymphosarcoma.

amenable to surgical treatment. However,

cally early lymphoma followed by prophylactic external irradiation have shown 5 year survival rates of approximately 25 per cent of patients. For lymphosarcoma of the head and neck, the results have been even better as Catlin reported a 5 year survival rate of 52 per cent. Hellwig's statistics also are of

tion

While the results of radical surgical removal are not as yet convincingly superior to intensive irradiation nevertheless this procedure does offer a chance of cure. Therefore, in carefully selected cases, extirpative surgery should receive serious consideration.

Roentgen Irradiation and Radium. Roentgen irradiation is the mainstay of treatment for the malignant lymphomas. It is used in treating either localized or generalized disease, high voltage being employed when deep penetration is desired. Radium now is used infrequently, although it is useful in the treatment of localized, superficial lesions.

Inasmuch as the clinical manifestations in this group of diseases vary tremendously, it is particularly important that treatment be individualized. Modifications in procedure must be adapted to the stage of the disease and the accessibility of the lesions. Here

case, these results are comparable to those obtained from local extirpation followed by irradiation. It should be remembered, however, that obliterative irradiation has undesirable late effects, such as fibrosis, telangiectasia, and irradiation dermatitis.

Craver, in a discussion of dosage for adequate treatment of early lesions, was of the opinion that the maximal dose tolerated by the skin overlying the lesion should be given in fractional increments.

For generalized disease, various areas are treated in succession unless irradiation of the whole body is employed. During periods of treatment, the condition of the patient and the effect on the blood and tissues must be watched. If the patient is receiving treatment every day or every second day, leukocyte counts should be obtained preceding each treatment. Irradiation is continued until all areas have been treated, unless leukopenia of severe degree or irradiation sickness with vomiting and dehydration develops. If either of the latter occurs, treatment should be discontinued temporarily or for a longer period, depending on the condition of the patient. Once remission has been induced, additional roentgen treatment should be withheld until definite signs of relapse occur, thus allowing for maximal recovery of normal tissues between courses of treatment.

Far advanced disease and large tumor masses do not respond as readily to irradiation as early or moderately advanced disease, or small, recently enlarged groups of lymph nodes. Under these circumstances, heavier irradiation will be required. However, after repeated courses of treatment, refractoriness to roentgen irradiation eventually develops. When this is encountered, the administration of one of the nitrogen mustards may result in temporary improvement.

Although the remissions induced by the nitrogen mustards rarely are complete and seldom last more than 3 to 12 weeks, repeated courses can be given each time a relapse occurs. Thus, the lives of many of these patients can be prolonged, and in some instances after intervals of several months roentgen irradiation may again become effective.

The results of irradiation of the whole body are expected.

Radiophosphorus. The use of this isotope is contraindicated in all cases of early and

in most cases of advanced malignant lymphoma, except possibly cases of far advanced disease with extensive involvement of the bone marrow. The administration of radioactive phosphorus is complicated by the development of thrombocytopenia and leukopenia, often of severe degree, long before maximal irradiation of diseased lymphoid tissue is achieved.

Nitrogen Mustards These compounds are halogenated alkyl or β chloroethyl amines all having the same fundamental chemical structure. When they are dissolved in polar solvents ethylenammonium derivatives are produced by intramolecular ionization, resulting in the liberation of a cyclic ammonium cation which has an action on cells and tissues similar to that produced by irradiation. These derivatives, and not the nitrogen mustards themselves, are cytotoxic. The two compounds most extensively studied so far are methyl bis (β chloroethyl) amine hydrochloride (HN_2) and tris (β -chloroethyl) amine hydrochloride (HN_3). Their mode of action is characterized by inhibition or inactivation of enzyme systems, inhibition of mitosis, and induction of chromosomal abnormalities.

The degree of response is roughly proportional to the dose employed, large doses affect virtually every cell in the body. However, rapidly growing cells, whether normal or neoplastic, are more susceptible to the cytotoxic effect of these compounds than slowly growing cells. Hematopoietic tissues are especially susceptible.

The action of the nitrogen mustards on the hematopoietic tissues is reflected by the development of leukopenia, associated at first with lymphopenia, and later with granulopenia. In some cases, thrombocytopenia and anemia also may develop. Lymphocytopenia may be apparent within 24 hours after the first injection of the drug and becomes progressively more severe for 8 to 10 days. Granulocytopenia develops gradually over a period of 2 to 3 weeks after a course of treatment, and the thrombocytopenia may be noted at this time also. Thereafter, blood counts gradually return to normal.

Nitrogen mustard compounds are stable in dry form, but unstable in aqueous solution. Fresh solutions, therefore, must be used

These are made by adding 10 cc of sterile isotonic solution of sodium chloride to sterile glass tubes or bottles, each containing 10 micrograms of the dry salt. Immediate injection of the fresh solution is important. Only the intravenous route of administration is employed. Considerable care should be taken to prevent these solutions from coming into direct contact with the skin or from escaping from the vein into the surrounding tissues.

The standard single dose now generally employed for the methyl bis and tris (β chloroethyl) amine compounds is 0.1 mg per kilogram of body weight. A course of treatment consists in most instances of three to six injections of either compound every day or every second day, the total dose thus varying from 0.3 to 0.6 mg per kilogram of body weight. Although treatment must be individualized, most patients will tolerate well a total dose of 0.4 mg per kilogram of body weight. While the total amount to be given for one course of treatment can be administered either in one or in two injections, complications, especially thrombophlebitis in the vein used for the injection, are more apt to occur when it is given in this manner. For doses of 0.1 mg per kilogram of body weight, the material may be injected directly into a vein, but for larger doses the incidence of thrombophlebitis can be lessened if the drug is injected into the rubber tubing of an intravenous apparatus during the course of an infusion of saline or glucose solution which is being delivered at a relatively rapid rate.

In three groups of cases of malignant lymphoma treatment with the nitrogen mustards appears to be specifically indicated. These are (1) cases of far advanced disease which has become refractory to irradiation therapy, (2) cases of acute disease failing to respond to roentgen irradiation and (3) cases of widespread systemic disease with extensive visceral involvement. The nitrogen mustards should not be used for early localized lymphoma or for moderately advanced systemic disease still responding well to roentgen therapy. Their use for giant follicle

dition is relatively benign and the risk of treatment outweighs the hazards of the disease itself

The nitrogen mustards are potentially dangerous drugs. Hence before using the

show that sensitivity to irradiation may be restored in occasional patients after successive courses of treatment with the nitrogen mustards

be both local and systemic. If extravasation of nitrogen mustard compounds occurs during injection, pain followed by a tender indurated swelling occurs at the site of injection and the latter resolves slowly. Early systemic effects are nausea and vomiting which occur in a high proportion of cases beginning 1 to 3 hours after injection and lasting several hours. However, not infrequently the nausea and vomiting subside after the first or second injection during a single course of treatment. Anorexia is less frequent and usually is transient. Diarrhea rarely occurs.

Delayed reactions are thrombophlebitis and thrombosis in the vessel used for the injection and widespread severe destruction of hematopoietic tissues. Hypoplasia or aplasia of the marrow may develop and the resulting thrombocytopenia may be accompanied by hemorrhagic phenomena. Death from cerebral hemorrhage occasionally occurs. Damage to organs such as the liver has not been demonstrated by special function tests (Hellwig).

The results of treatment with the nitrogen mustards appear to be somewhat more favorable in Hodgkin's disease than in some of the other forms of malignant lymphoma. Rhoads reported that approximately 70 per cent of the patients treated show objective improvement and 90 per cent subjective improvement. There are failures. Remissions are of short duration lasting from 1 to 3 months rarely as long as 6 months. They can be induced not only once but in many cases many times with subsequent courses of treatment. Patients whose condition has become refractory to roentgen irradiation may respond favorably and sometimes dramatically to treatment with this compound. Moreover, there is now some evidence to

are more common. Severe toxic reactions are more prone to occur and an increasing resistance to successive courses of therapy is more likely to be encountered. In mycosis fungoides, nitrogen mustard therapy has been found to be a useful adjunct to roentgen irradiation also (Kierland et al., Henstell et al.).

General Measures. These are essentially the same as those outlined for chronic granulocytic leukemia.

BYRON E. HALL

REFERENCES

- Cutler D. Quoted by Craver.
Craver L. F. Lymphomas and Leukemias. Value of Early Diagnosis and Treatment. *JAMA* 136:244, 1948.
Gall E. A. Surgical Treatment of Malignant Lymphoma. *Ann. Surg.* 118:1064, 1943.
Gilman A. and Phillips F. S. Biological Actions and Therapeutic Applications of β -Chloroethylamine. *J. Clin. Oncol.* 1:1, 1947.
Graef I. et al. Clinical and Pathologic Effects of Nitrogen Mustard. *J. Clin. Oncol.* 1:1, 1947.
Hellwig. *Obst. Gynecol.* 1947.
Press. 1947.
Kierland H., Watkins C. H., and Shullenberger C. C. Use of Nitrogen Mustard in Treatment of

- Mycosis Fungoides J Invest Dermat* 9 195
1947
- Verner T B and Stenstrom A W Roentgen
Therapy in Hodgkins Disease *Radiology* 48
355 1947
- Rhoads C P Recent Advances in Treatment of
Cancer *JAMA* 136 305 1948
- Roswit H and Kaplan G The Role of Nitrogen
Mustard (HN_2) as a systemic Adjunct to the
Radiation Therapy of Certain Malignant Diseases
Am J Roentgenol 61 626 1949
- Shullenberger C C Watkins C H and Kierland
R R Experiences with Nitrogen Mustard Ther-
apy *JAMA* 139 73 1949
- Spurr C L et al The Clinical Application of
Methyl Bis (2 Chloroethyl) Amine Hydrochloride
to the Treatment of Lymphomas and Allied
Dyscrasias Approaches to Tumor Chemotherapy
Washington D C American Association for
Advancement of Science 1947
- Stout A P Results of Treatment of Lympho-
sarcoma *New York State J Med* 47 159 1947
- Sugraker E D and Craver L F Lympho-
sarcoma Study of 196 Cases with Biopsy
JAMA 115 17 112 1940
- Wintrobe M M and Huguley C M Jr Nitro-
gen Mustard Therapy for Hodgkins Disease
Lymphosarcoma the Leukemias and Other Dis-
orders *Cancer* 1 357 1948
- Wintrobe M M et al Nitrogen Mustard as
Therapeutic Agent for Hodgkins Disease
Lymphosarcoma and Leukemia *Ann Int Med*
2 529 1947

POLYCYTHEMIA VERA

Polycythemia vera is a chronic disease with protean manifestations which not infrequently are associated with other disease processes for example gout duodenal ulcer arterial occlusive disease and so forth. Although no cure is known for it the primary aim of treatment is (1) control of the disease itself and (2) control or alleviation of associated disorders.

Control of the primary disease may be accomplished by reducing the total blood volume through (1) withdrawal of blood (venesection) (2) destruction of erythrocytes by administration of phenylhydrazine or (3) interference with production of blood by use of roentgen therapy radiophosphorus chemical agents or the administration of a diet low in blood building substances especially iron. In selecting what form of treatment to employ, it is advisable to keep in mind the major complications of this disease thrombosis and hemorrhage. The increased blood volume erythrocyte and platelet counts and viscosity lead to slowing of blood

flow and predispose to thrombosis the principal cause of death. The increased blood volume associated with distention of blood vessels often leads to hemorrhage the next most common cause of death. Treatment, therefore should be directed toward the reduction of those factors which predispose to thrombosis and hemorrhage.

Venesection Venesection long employed as a method for treating polycythemia vera is preferred by many clinicians to other

technical difficulties of withdrawing blood of increased viscosity and (2) the difficulty of maintaining the patient in satisfactory remission over long periods of time.

Venesections on polycythemic patients are facilitated by adherence to a few simple rules. Clotting of blood in the needle is less likely to occur if a large gauge needle (15 gauge) and suction (vacuum bottle) are employed. Of even greater importance is the introduction of the needle into the vein against the direction of blood flow so that a direct flow of blood from the vein through the needle occurs. Cutting down on veins for the purpose of inserting the needle should be avoided except in emergencies because the subsequent development of scar tissue frequently precludes the use of these veins for future venesection. Quantities of 500 to 700 cc are withdrawn at intervals of 1 or 2 days until the volume of erythrocytes has been reduced to normal.

Maintenance therapy should be instituted after a normal cell volume has been established. This consists simply of periodic examinations of blood and the performance of venesections as often as necessary to maintain a normal cell volume. The frequency with which venesections should be performed will vary from patient to patient hence the interval between examinations of the blood must be individualized for each patient. Not infrequently remissions lasting weeks or months will be noted after a normal volume of erythrocytes has been established from the initial series of venesections.

Polycythemia vera of mild degree can be controlled by means of venesections alone provided that the patient understands the nature of his illness and the importance of

adequate control Polycythemia vera of severe degree presents a more difficult problem because the individual requiring frequent venesections often becomes discouraged and fails to co operate fully with his physician In cases of this type the utilization of forms of therapy offering the patient hope of remissions of long duration would appear to be justified Dameshek and Henstell advocated the production of a chronic iron deficiency by means of repeated venesections and adherence to a diet low in iron Treatment of polycythemia vera by withdrawal of massive quantities of blood and transfusions of plasma has also been suggested (Widstrom and Swedberg)

Phenylhydrazine The oral administration of phenylhydrazine is effective in controlling polycythemia vera in many but not all cases This drug ($C_6H_5NHNH_2$) is prepared from aniline and is related to antipyrine Crystalline phenylhydrazine or acetylphenylhydrazine should be used since liquid phenylhydrazine is unstable Both compounds are equally effective and are generally given in the form of capsules

The action of phenylhydrazine on the blood presumably is hemolytic the degree of hemolysis obtained being proportionate to the dose administered The administration of the drug is followed by neutrophilic leukocytosis decrease in erythrocytes increase in plasma bilirubin reticulocytosis and diminution of the total blood volume If destruction of the blood is sufficiently pronounced nucleated erythrocytes may appear in the circulation

As originally employed phenylhydrazine was utilized to reduce the total blood volume Doses of 0.1 gm were given two or three times daily until evidence of active hemolysis was observed or until a total of 30 to 40 gm had been administered Since a number of deaths were encountered principally from acute hemolytic anemia or the development of thrombotic phenomena the use of phenylhydrazine as the initial form of treatment was avoided for patients more than 60 years of age for patients confined to bed for patients with advanced arteriosclerosis or visceral disease and for patients who had a history of thrombosis After a normal cell volume had been achieved maintenance therapy consisted of the administration of

0.1 to 0.3 gm of phenylhydrazine each week

Treatment with phenylhydrazine to reduce the blood volume is seldom employed now since restoration of normal blood volume can be accomplished initially far more safely by means of repeated venesections However once the blood volume has been restored to normal as a maintenance measure 0.1 to 0.4 gm weekly can be given to patients who tolerate the drug Ordinarily 0.1 gm of phenylhydrazine is given by mouth three times a day on one day only of each week

The principal disadvantages of maintenance therapy with phenylhydrazine are (1) intolerance of many patients to the drug the most common symptom being nausea and (2) its failure to lower significantly the incidence of thrombotic phenomena

Roentgen Irradiation Of the various forms of roentgen irradiation that have been used total body irradiation ("spray therapy") is the most successful Roentgen therapy to the spleen not only fails to induce remissions but seldom significantly diminishes the size of this organ Irradiation of the bone marrow (systemic treatment of the principal bones containing red marrow) is more effective but the results frequently are transitory Since 1932 when Sgalter first reported encouraging results from irradiation of the entire body a number of reports have appeared The report of Richardson and Robbins is impressive Of 23 patients treated over a period of 15 years therapeutic failure was noted in only one instance Remissions lasting from 15 to 55 years were obtained in a small number of cases from one course of treatment In most cases however multiple courses of treatment were required to control the disease At the end of the period of observation 16 patients were living and 12 had died The survival time in the latter group ranged from 15 to 11 years with an average of 5.6 years Four patients in this group died of causes not attributable to the polycythemia The survival time among the patients still living ranged from 15 to 9 years with an average of 5.4 years

From the results obtained by Richardson and Robbins and others spray irradiation appears to be an effective method for controlling polycythemia vera The chief disadvantages of the method are (1) the need for

the roentgen therapist to possess special and expensive equipment, (2) the time required for one course of treatment, (3) the discomfort to the patient of roentgen sickness, and (4) the possibility of injurious immediate or long range effects. Refractory anemia and acute leukemia developing as a terminal event in polycythemic patients who have received whole body irradiation have been reported. Whether roentgen therapy can be incriminated as causing the development of acute leukemia in patients having polycythemia vera is problematic, since this condition, although rare, has been observed as a terminal event in polycythemic patients who had not been treated with irradiation in any form. In any case, the occurrence of refractory anemia or acute leukemia is sufficiently unusual that neither of these conditions need be considered a contraindication to the use of spray irradiation in patients having severe or moderately severe polycythemia vera.

Radiophosphorus The administration of radioactive phosphorus to patients having polycythemia vera in relapse is highly effective in controlling this disease. Remissions, often of long duration can be induced in a high percentage of patients, and the incidence of the major complications of the disease can be reduced materially. While the results of treatment are sufficiently impressive to suggest that this method is superior to other methods currently in use, emphasis should be placed on the fact that the long-range effects of introducing radioactive phosphorus into the human body have not been determined. The possibility of the development of neoplastic disease, especially acute leukemia, in a small number of patients treated with radioactive phosphorus has been a subject of grave concern. Although the incidence of acute leukemia is slightly higher among patients treated with radioactive phosphorus than among those treated by venesections or the administration of phenylhydrazine, the incidence of thrombosis, hemorrhage, and a terminal chronic leukemic picture is significantly less. Hence, the hazards ascribed to treatment with radioactive phosphorus appear to be materially less than those associated with uncontrolled or only partially controlled polycythemia. However, until the long range effects of

treatment with radioactive phosphorus are known, it would seem advisable to restrict this form of treatment to use in those cases in which polycythemia is not easily or well controlled by other means.

Radiophosphorus should be administered only by physicians experienced in its use. The isotope is distributed under the auspices of the Isotopes Branch of the U S Atomic Energy Commission to properly trained physicians who have available to them requisite laboratory equipment for measurement and handling.

Radioactive phosphorus has a half life of 143 days. It emits only beta rays, which have a maximal range of penetration in tissues of approximately 7 mm, and an average range of penetration of about 2 mm. Thus irradiation is confined primarily to those tissues in which radioactive phosphorus is deposited. The isotope may be given orally or parenterally. When given orally, approximately 75 per cent is absorbed from the gastro intestinal tract (Reinhard et al). Although the amount lost by fecal excretion is not constant, it is generally safe to add 25 per cent to the calculated parenteral dose if one wishes to administer the isotope by mouth.

When radioactive phosphorus is administered intravenously, from 5 to 25 per cent of the administered dose is excreted in the urine in the first 4 to 6 days. The portion not excreted is deposited in bone marrow, lymph nodes, liver, spleen and later in bone. Rapidly growing cells incorporate more radioactive phosphorus than slowly growing tissues. Thus, greater amounts of radioactive phosphorus are deposited in rapidly growing leukemic cells than in normal cells. Because radioactive phosphorus is deposited primarily in bone marrow and later as phosphate in bone, this isotope is highly effective for irradiating the bone marrow. Inhibition of hematopoiesis is thereby accomplished. However, the inhibitory effect of radioactive phosphorus on erythropoiesis in patients having polycythemia vera may not be discernible in less than 2 to 3 weeks after the administration of the initial dose. The life span of the erythrocyte is in the neighborhood of 90 to 120 days, and since radioactive phosphorus does not destroy erythrocytes several weeks must elapse before erythro-

cytes age and are removed from the circulation

The method my colleagues and I employ in treating patients with polycythemia vera in relapse is as follows. Duly venesections are performed until the cell volume (hematocrit) has been lowered to 55 per cent or less. This is done to diminish the risk of the development of thrombotic phenomena in the interval between the administration of radioactive phosphorus and the period several weeks later when the inhibitory effect of radioactive phosphorus on hematopoiesis becomes manifest. Then, a single intravenous injection of from 3 to 7 millicuries of radioactive phosphorus is administered, the size of the initial dose being based on the apparent clinical severity of the disease. In most cases, initial doses of from 5 to 6 millicuries are employed. The patient is then instructed to have the blood examined at intervals of 4 and 6 weeks, and to return at the end of 8 to 12 weeks for a second injection of radioactive phosphorus if a remission has not been induced. Leukocyte and platelet counts, in addition to determination of cell volume and an erythrocyte count, should be made before the administration of the second dose. If leukopenia or thrombocytopenia of severe degree has developed the administration of additional radioactive phosphorus should be withheld until the leukocyte or platelet count has returned to values approximating normal. If leukopenia or thrombocytopenia of mild or moderate degree is found the size of the second dose should be smaller than the first. However, in those cases in which neither leukopenia nor thrombocytopenia is encountered the size of the second dose may approximate the first. The same plan as that after the first injection is then followed for later injections, a third, fourth, and even a fifth injection may be given at intervals of 2 to 3 months until a remission has been induced.

In experience at the Mayo Clinic, radioactive phosphorus therapy is highly successful if proper co operation between patient and physician is established. It is important to instruct the patient in the necessity for re examinations of the blood at regular intervals after the initial treatment. Remissions may be expected after one injection of radioactive phosphorus among approximately a third of

all the patients treated, and after two injections among another third. The remaining third may require from three to five injections. Remissions may last from 6 months to 6 years, the average in our series of cases was from 18 to 24 months (Hall).

The most common complications encountered as a result of treatment with radioactive phosphorus are the development of leukopenia, thrombocytopenia, and anemia. As a rule, these are not serious, and recovery is complete in the course of a few weeks if no further treatment is given. Severe hypoplasia of the bone marrow may result from overdosage, or rarely, from the administration of amounts of radioactive phosphorus of therapeutic magnitude. When hypoplasia of the marrow is encountered treatment consists of the administration of blood transfusions at periodic intervals until erythropoiesis again becomes active. This may require several months.

The advantages of radioactive phosphorus therapy are the simplicity of the method, the ease of administration, the absence of irradiation sickness, and the reduced incidence of the major complications of polycy-

leagues and I believe is offset by the marked reduction in the incidence of thrombosis and hemorrhage, the occasional development of severe hypoplasia of the marrow, and the fact that the long range effects of treatment with radioactive phosphorus are unknown.

However, as Lawrence has shown, the survival time of polycythemic patients treated with radioactive phosphorus is comparable to that of patients under treatment for diabetes mellitus or pernicious anemia.

Nitrogen Mustard Methyl bis (β chlor ethyl) amine hydrochloride (HN_2) has been used in the treatment of polycythemia vera. Remissions may be induced with total dosages of from 0.4 to 0.6 mg per kilogram of body weight, but they are usually of much shorter duration than the remissions induced by radioactive phosphorus. Relapses are common in from 3 to 6 months after the initial course of treatment, and rarely do the remissions last more than a year. This form of treatment does not appear to have any

to shorten the convalescence. Operations on joints should be undertaken only in unusual circumstances as a calculated risk with a high chance of failure and possible exsanguination.

Small wounds are best treated locally with thrombin which precipitates fibrin instantly. Such wounds must be clean, as the topical agent must be brought into direct contact with the bleeding surface. A sustained pressure dressing may be used concomitantly. Cautery may temporarily stop the bleeding, but a subsequent slough is likely to form and bleeding will again ensue, this time from a larger area. Extractions of teeth are hazardous and may be fatal.

The care of these patients is directed toward the preliminary reduction of the patient's coagulation time to as near normal as possible with transfusions of blood or antihemolytic globulin, local measures to control bleeding, and repeated small transfusions of blood as necessary during the period which bleeding may occur. Thrombin or dried plasma may be applied locally, a partial denture may be used as a pressure dressing, or a bloodless extraction may be attempted by the rubber band method.

Blood transfusions, which need not be large to be effective, continue to be most successful in lowering the coagulation time to normal. Fresh whole blood or plasma are the most dependable, but stored blood and stored, frozen, or lyophilized plasma are also effective. The quantity transfused will depend on how much blood has been lost and must be replaced as well as on how much blood is necessary to restore the coagulation time to normal. If whole blood is not available or unnecessary, 100 to 250 cc of plasma may be administered for its anti-hemophilic qualities alone. This effect persists for 8 to 12 hours and is maximal in one hour.

In more recent years, particularly during the . . .

... have been almost as effective as fresh whole blood in shortening the coagulation time. However, a refractory state may develop with its repeated use. This is less apt to occur from the use of blood or blood plasma.

Injectations of fresh and lyophilized plasma twice weekly have been used prophylactically with prolongation of the interval between hemorrhage.

The mortality rate from major operations in cases of hemophilia is inordinately high, and operation should be avoided whenever an alternative exists. The acute abdomen has long constituted one of surgery's imperative emergencies. Recently, however, antibiotics in adequate amounts have greatly lessened the risk of peritonitis, thus permitting safe observation over a somewhat longer period of time, ultimately, perhaps, even obviating the need for surgery altogether.

It is also clear that in many cases of peritonitis, acute appendicitis and occasionally even intestinal obstruction are simulated by or due to retroperitoneal or submucosal hemorrhage. Thus, the decision to operate is beset by many difficulties and the need for temporizing is emphasized.

If, however, operation is considered to be unavoidable, the coagulation time should be brought as nearly to normal as possible, blood should be given freely in small amounts at frequent intervals, and a local hemostatic agent, such as thrombin, used with the customary careful surgical methods.

EDWIN D. BAYRD

REFERENCE

Davidson C S et al. Hemophilia. A Clinical Study of 40 Patients. *Blood* 4:97, 1949.

PURPURA

Idiopathic Thrombocytopenic Purpura. The value of any therapeutic measure must inevitably be considered in relation to the natural history of the disease. This is true in idiopathic thrombocytopenic purpura, a cyclic disease, tending to spontaneous remissions. A gradient from young to old may be noted. The young are most frequently affected, most frequently undergo spontaneous remissions, and are most benefited by accepted therapy. The disease becomes increasingly uncommon among persons more than 30 years of age and rare among those more than 50 years of age. In addition, it must be noted that adult males are seldom affected.

It may seem superfluous to reiterate the

repeated injunction, "be certain of the diagnosis," yet even the experienced observer may be deceived by clinical appearances and saved only by confirmation of the diagnosis by observations of the bone marrow. With the technic of sternal aspiration so highly developed, probably no patient should be subjected to splenectomy without this having first been done.

Approximately 35 to 40 per cent of patients may be expected to undergo permanent spontaneous remissions. This is particularly true of infants. Obviously any form of treatment will be effective in this group.

The rest may temporarily improve, fail to improve, or progress rapidly to a fatal issue.

though platelets agglutinate shortly after withdrawal of blood from the blood bank may be used successfully. Apparently the agglutinated platelets are still functionally active. However, fresh blood is to be preferred. The amount of blood given will depend on the physician's preference as well as the patient's condition. Generally speaking, transfusions of 500 cc of blood are tolerated well if the rate of delivery is not too fast.

Transfusions may be used preoperatively to prepare a patient who is severely ill for splenectomy or to protect a patient during his first episode when operation is refused or for other reasons a conservative course is pursued.

Allen and his associates described the occurrence of a heparin like substance in idiopathic thrombocytopenic purpura which responded to an inhibitory effect of antihypertensive toluidine blue or protamine administered intravenously. Either was administered in daily doses of 1 to 4 mg per kilogram of body weight in 250 to 500 cc of normal saline solution over a 2 hour period. More recently larger doses have been used. An initial dose of 25 mg per kilogram of body weight was usually satisfactory. A dose of 15 to 2 mg per kilogram was given thereafter until bleeding stopped (usually in 24 to 48 hours) after which time it was administered every 2, 3, or 4 days, or as bleeding recurred.

Our own experience with this method has been discouraging and we have not been able to duplicate the proponents' good results.

Other methods of treatment, including the use of snake venom, testosterone, vitamins and so forth are of doubtful value. A diet high in protein and supplementary iron should be employed if loss of blood of any significant degree occurs.

Splenectomy, as it becomes safer with improved methods, assumes a more prominent place in the therapy of this disease. Elliott reported no operative deaths in a series of 62 splenectomies for this disease. Curtis had one death in 22 consecutive splenectomies for thrombocytopenic purpura. The long time operative mortality—in the cases observed at the Mayo Clinic has been approximately 5 per cent. The eventual mortality in cases in which splenectomy is not carried out is probably in excess of 12 per cent. Except for the risk of splenectomy which is approaching a negligible figure, the

patient temporized with too long. It is held that the finding of eosinophilia of the bone marrow indicates a more favorable prognosis with a tendency to spontaneous recovery. This is not infallible, however, as we have observed a fatal outcome from cerebral hemorrhage in such a case in which splenectomy was too long deferred.

Elliott noted successful results among 95 per cent of patients less than 31 years of age on whom splenectomy was done. Among those 31 or more years of age only 43 per cent obtained good results, making an overall figure of 77.4 per cent good results, twice the 36 per cent good results for patients treated medically. This compares well with the figures presented by Curtis, Wintrobe, and investigators at the Mayo Clinic.

After splenectomy thrombocytopenia may persist with or without bleeding or after an initial rise in platelets, thrombocytopenia may recur. When it occurs, it presents an exceedingly distressing problem. Accessory splenic tissue has been implicated frequently and in at least one instance apparently removed with benefit. Attempts at the clinic have not been so gratifying. In one instance,

five accessory spleens of fair size were delineated preoperatively with thorotrast and all subsequently removed at operation with out, in the least, affecting the unfavorable course. In another case exploratory operation was performed without accessory splenic tissue being found. Following a turbulent post-operative course, a satisfactory remission occurred which has persisted for more than a year. All decisions in such cases are perilous and uncertain.

Secondary Thrombocytopenic Purpura
Secondary or symptomatic thrombocytopenic purpura occurs in conjunction with some other primary disease or disturbance. Among these are the blood dyscrasias (the leukemias, lymphomas, multiple myelomas, aplastic and pernicious anemia), metastatic malignant lesions, Gaucher's disease, acute infections, hepatic disease, hypersplenism, and drug intoxication. The following drugs and chemical agents are known to precipitate thrombocytopenic purpura: organic arsenicals, gold salts, benzene, allyl-isopropyl acetyl-carbamide (sedormid), dinitrophenol, quinine, ergot, sulfonamides, thiourea and sodium salicylate.

Treatment is directed toward the correction or amelioration of the underlying process. Contact with possible offending drugs or chemical agents should be removed. Blood transfusions may be of temporary benefit in the control of bleeding if it becomes a problem. Splenectomy is of value in Gaucher's disease associated with a secondary thrombocytopenic purpura, in hypersplenism, and occasionally in cases of lymphoma with thrombocytopenia.

BAL in adequate amounts is of proved value in the treatment of thrombocytopenic purpura resulting from heavy metal poisoning such as occasionally occurs in chrysotherapy or antisyphilitic treatment with organic arsenicals. Splenectomy has been performed successfully in such cases.

Sedormid causes thrombocytopenic purpura in individuals sensitive to it, although, in the early stage, the bone marrow may show no depletion of megakaryocytes.

Thrombotic Thrombocytopenia Since 1925, 14 cases of acute purpura with associated platelet thrombi, thrombocytopenia and fever, anemia, and a rapidly progressive fatal course have been reported (Fitzgerald

et al.) Of the patients affected, 11 have been females, 3 males, 11 were 34 years of age or younger. Splenectomy was done in 2 instances without success. The cause is not known and no effective form of treatment has been found.

Nonthrombocytopenic or Vascular Purpura
Capillary purpura due to allergy (Schönlein-Henoch purpura), an inadequately understood syndrome, results from increased permeability of the capillary bed. Hematopoiesis is undisturbed. Symptoms occur whenever exudation takes place. The skin, gastro-intestinal tract, and joints are most frequently involved. If an underlying cause can be discovered, it should be removed. Adrenalin 0.5 to 0.1 cc of 1:1000 solution given subcutaneously may be of help in relieving the skin manifestations, calcium salts intravenously may relieve intestinal symptoms.

Recurrences are common, but the prognosis is generally good, although extensive hemorrhage into a vital center can occur. Since vascular purpura is essentially an affliction of children and young adults, improvement may occur spontaneously with advancing age.

Purpura simplex is a benign hereditary familial disturbance affecting all parts of the body, but principally the extremities. It may come on at any age, occurs chiefly in women, and needs no treatment.

Symptomatic vascular purpura may be due to trauma, senility, orthostasis, infection, liver disease, avitaminosis, snake venom, and drugs. Treatment consists of recognition and removal of the underlying process.

EDWIN D. BAYRD

REFERENCES

- Allen, J. G., et al. Abnormal Bleeding Response to Treatment with Toluene Blue and Protamine Sulfate. *JAMA*, 139:1251, 1949.
- Allen, J. G., et al. Some Observations on Bleeding Tendency in Thrombocytopenic Purpura. *Ann Int Med*, 27:382, 1947.
- Davis, E. Schönlein-Henoch Syndrome of Vascular Purpura. *Blood*, 3:129, 1943.
- Elliott, R. H. E., Jr. Reevaluation of Splenectomy in Thrombocytopenic Purpura, Based on 27 Year Combined Clinic Follow-up Experience (Lewis Linn McArthur Lecture). *Proc Inst Med Chicago*, 16:330, 1947.
- Fitzgerald, P. J., Auerbach, O., and Frame, E. Thrombotic Acroangiothrombosis (Platelet

Thrombosis of Capillaries Arterioles, and Venules) *Blood*, 2 519, 1947
 Parkin T W Hall, H E and Watkins C H
 Experience with Antiheparin Compounds in Essential Thrombocytopenic Purpura *Proc Staff Meet, Mayo Clin* 23 309, 1948

MULTIPLE MYELOMA

Myeloma a plasmacytic neoplasm involving the bone marrow and to a lesser degree the viscera, may be observed in a localized generalized or leukemic form Its treatment has always been an exceptionally distressing problem for doctor and patient alike as it is not only a uniformly fatal disease but often an agonizingly painful one Palliation of the symptoms management of the complications and specific treatment will be considered

Pain is the most prevalent most distressing and most difficult symptom to control A number of general measures have been employed with varying success against it Their relative values in any group of cases are unimportant since they cannot be used as a basis for predicting individual responses

Roentgen therapy the oldest method of treatment is the most widely used It is the treatment of choice in local lesions, best used in conjunction with surgical excision if the lesion is accessible For the diffuse disease it is often helpful in relieving distress and occasionally will be accompanied by regression of bone lesions In cases in which its effectiveness has been demonstrated it may be repeated several times with benefit The development of leukopenia however, may prevent its use

Radiophosphorus has about the same range of usefulness as roentgen rays in the generalized form of the disease We have seen one patient in a terminal stage of the leukemic phase undergo a remission following the administration of a little over 60 millicuries of this drug It has been our practice to administer 15 to 25 millicuries of radiophosphorus intravenously each week until improvement occurs or neutropenia begins to develop It has no unpleasant side effects, is easy to give but possible suppression of the bone marrow is a risk to be appreciated

4 4' Diamidinostilbene (stilbamidine), 4,

4' - (pentamethylenedioxy) dibenzamidine (pentamidine), and antimony, parenterally administered, have also produced relief of pain in some patients Stilbamidine has been most widely used (Snapper) As advocated, this drug is dissolved in 10 cc of sterile distilled water and injected intravenously 30 minutes after the patient has received a hypodermic injection of $\frac{1}{150}$ gram (0.00043 gm) of atropine Fifty milligrams are given the first day, 100 mg the second and 150 mg daily thereafter in conjunction with a diet low in animal protein Good results in some cases have also been obtained without dietary restrictions A course consists of 20 injections, but may be repeated Its use is contraindicated in the presence of renal failure

Immediate unpleasant side effects, minimized by atropine, may include burning paresthesia formation, nausea, vomiting unconsciousness, and convulsions A late side effect (25 to 5 months later) is trigeminal neuropathy with burning itching and dissociated anesthesia This usually subsides spontaneously but may persist for months

Injections of procaine or dolamin may be helpful in blocking pain of a restricted distribution Orthopedic measures, such as the use of a Taylor brace or belt and reduction of pathologic fractures, are often necessary Laminectomy may relieve transverse myelitis Daily water diuresis may protect a patient with Bence Jones proteinuria from "nephron nephrosis," and blood transfusions are useful in relieving the anemia Once uremia develops, the outlook is critical

Until recently there was no specific treatment for this disease However, confirmation of Alwall's observation of a complete clinical and hematologic remission following the prolonged use of urethane in one of 2 cases of multiple myeloma has stimulated renewed interest in this drug which is at present the agent of choice About 50 per cent good results are claimed There can be no doubt that in some cases complete remission has resulted

Fairly large doses of urethane (3 to 6 gm daily) of either the elixir or coated tablet are advocated This must be continued for 4 to 8 weeks at which time the dose may be reduced or discontinued, depending on

the patient's response and the development of leukopenia. The primary objective should be a sustained high level of the drug over a long period of time. Although good results have been reported with smaller doses and

other form of therapy offers the possible benefits of urethane at present

EDWIN D. BAYRD

REFERENCES

- Alwall N. Urethane and Stilbamidine in Multiple Myeloma. Report on 2 Cases. *Lancet* 2:338, 1947.
- Bayrd E. D. and Hall H. E. Unusual Remission After Radiophosphorus Therapy in a Case of "Acute Plasma Cell Leukemia." *Blood* 3:1019, 1948.
- Loge J. P. and Rundles R. W. Urethane (Ethyl Carbamate) Therapy in Multiple Myeloma. *Blood* 4:201, 1949.
- Snapper I. Stilbamidine and Pentamidine in Multiple Myeloma. *JAMA* 133:157, 1947.

this for at least 3 months. Even so, we have found large doses of urethane to be poorly tolerated and have been generally disappointed with the results in most of our patients. One has received more than 1000 gm without appreciable effect on his disease. Nevertheless, despite the uncertainties, no

DISEASES OF THE URINARY TRACT

The treatment of renal diseases is still in a state of uncertainty because the pathologic physiology of renal diseases has not been fully worked out. The treatment therefore, must be largely symptomatic. In the past, it was well recognized that a damaged kidney was to be given rest by certain dietary re-

day with a better knowledge of kidney function the fundamental basis of treatment still is the reduction of the work of the kidney, by dietary measures.

What will be said in the following pages regarding the treatment of kidney diseases, while not absolute will give the reader an indication of the clinical methods used to combat the disorders. When a patient is in need of aid a physician is called on to use his clinical experience as a guide to therapy despite the controversy on the theory of the disease itself.

ACUTE GLOMERULONEPHRITIS

Volhard pointed out long ago that time is the most important factor in the treatment of acute glomerulonephritis. While acute nephritis may commence abruptly with the clinical features of hypertension or acute renal or cardiac insufficiency, there are also cases of slow development in which the patient complains of headache, anorexia, and fatigue, and at times of nothing at all. It is necessary, therefore, to be on the alert for acute nephritis after acute tonsillitis and other infections just as formerly we were after scarlet fever.

The treatment of acute glomerulonephritis may be divided into two categories: (1) the treatment of the abrupt, stormy type of the disease, and (2) the treatment of the milder forms. Only a comparatively small number of patients ever suffers from the form which begins abruptly and runs a stormy course.

The milder kind is more common, and the chief dangers of genuine uremia, convulsions and heart failure are rare in these milder types.

Treatment of the Abrupt, Stormy Type
The principal therapeutic measures in the abrupt phase of nephritis are control of high blood pressure, convulsions, heart failure and promotion of a diuresis to ward off uremia.

Hypertension per se seldom does direct damage but indirectly it may be the motivating factor causing pronounced edema of the brain with convulsions or sudden heart failure. Blackfan showed, in 1923, that blood pressure may be lowered and convulsions controlled by the intravenous use of 1 per cent magnesium sulfate. Today this is accomplished by giving 15 to 30 grains (2 to 3 gm) of magnesium sulfate two or three times a day depending on the clinical condition and requirements of the case. Rubin and Rapoport have reported favorable results with the administration of 45 grains (3 gm) of magnesium sulfate dissolved in 120 cc of 5 per cent glucose solution twice a day or oftener, depending on the blood pressure and the general condition of the patient. If possible, it is well to determine precisely the level of the magnesium in the blood. Occasionally, following the use of magnesium sulfate, respiratory embarrassment may occur, and it is necessary, therefore to have calcium gluconate ready for intravenous injection to combat the magnesium sulfate action. This may be given in doses of 30 grains (2 gm) in 50 cc of 5 per cent glucose, or two 10 cc ampules.

several times a day. Chloral hydrate or sodium bromide, 30 grains (2 gm), may also be dissolved in 200 cc of water and given by rectum by the Murphy drip method.

Myocardial failure is a common complication in acute nephritis especially when high blood pressure is present and digitalis $\frac{1}{2}$ grains (0.1 gm) intravenously three times a day or strophanthin $\frac{1}{100}$ grain (0.0006 gm) intravenously intramuscularly or subcutaneously repeated every 2 hours for four or five doses may be given Purified glycosides of digitalis such as digitoxin or digoxin both in doses of 0.25 mg or any of the other standard preparations may be used instead of digitalis Caffeine sodium benzoate 3 grains (0.2 gm) every 3 hours intramuscularly or subcutaneously has been used but I feel that it is not nearly so satisfactory as digitalis or strophanthin When heart failure sets in especially if hypertension attends it a venesection of 500 cc of blood may be of value

As there is always an increase of the blood volume in acute nephritis the administration of intravenous fluids must be given with great caution for the addition of fluid to the already overloaded vascular system may provoke an attack of heart failure Once heart failure sets in in such cases it is difficult to reverse or correct It is far better to take the proper measures to prevent the onset of an attack

If the kidneys cannot be made to function again or if oliguria or anuria does develop uremia may be imminent unless diuresis can be established Of most importance as a diuretic agent is water but other simple diuretics may be used such as potassium citrate 20 grains (1.3 gm) three or four times a day or a combination of potassium acetate and potassium citrate each 20 grains (1.3 gm) three or four times a day or a combination of potassium acetate and potassium citrate each 20 grains (1.3 gm) three times a day in liquor ammonii acetatis Stronger diuretics are contraindicated in the treatment of acute nephritis

Frequently when a patient is unable to take adequate fluids by mouth consideration must be given to the use of intravenous fluids The kind and amount to be given may be summarized briefly as follows (1) Whole blood plasma or albumin when severe anemia or reduction in plasma protein occurs this however is seldom used as the anemia in acute glomerulonephritis is not so severe (2) Physiologic saline when there is

hypochloremia or alkalosis due to vomiting and dehydration Alkalosis is rare in acute nephritis is acidosis usually develops usually 1000 cc every 12 hours for a few doses is sufficient to correct this abnormality (3) Glucose solutions 5 10 and 50 per cent the weaker ones when there is dehydration and it is necessary to replenish body fluids and the strongest solution when dehydration and diuresis are desirable (4) Alkaline solutions such as sodium bicarbonate 7.5 per cent intravenously and $\frac{1}{2}$ molar sodium lactate 1000 cc daily or more as necessary in the presence of acidosis as determined by a CO_2 combining power of below 40 vol per cent (5) Calcium chloride solutions or ammonium chloride solutions to combat alkalosis It must be emphasized again that when heart failure is imminent one must inject intravenous solutions slowly if at all as the danger of intravenous fluid to the heart depends more on the speed of administration than on the volume or kind of fluid administered

Attempts have been made to revive a method advocated by Volhard and called the "water thrust" in which 1200 to 1500 cc of water or weak tea are given within a period of a half hour if starvation and other methods of treatment fail to promote diuresis This method however has not been popular with most observers

There is no rigid rule regarding the restriction or administration of fluids but my observations have led me to restrict fluids if a patient has hypertension with increased intracranial pressure and to administer as much as 2000 cc a day if these clinical findings are not present If the nonprotein nitrogen has risen and an oliguria is becoming more accentuated fluids may be given in optimal amounts When there is a kidney shut down it is not logical to force fluids intravenously as damage may result when attempting to do so When hypertension

cases is to improve the urinary output which in turn augments the output of nitrogenous substances When there is no satisfactory response to the administration of intravenous fluids they should not be forced

Edema is not the criteria on which to base the administration or restriction of fluids as in cases without hypertension but with oliguria and rising nonprotein nitrogen fluids are given in spite of edema

Treatment of the Milder Form In the milder forms of the disease complete bed rest until the kidney lesion is healed and a regulated diet with special attention to the protein salt and fluid intake are most important to consider

The main factor in the treatment of the kidney lesion of nephritis is of course rest and other methods of treatment employed aim to bring about the fulfillment of this requirement. The importance of rest is difficult to visualize in the management of nephritis because there is no pain and no apparent unfavorable consequence of exercise. Rest for the inflamed kidney is accomplished by reducing the amount of exercise and work the patient is required to do thereby cutting down the metabolic requirements of the body which relieves the work load of the kidney. Murphy and Peters emphasized the importance of rest in an investigation of 89 patients with acute nephritis. Forty one were completely cured when they remained in the hospital until well while 48 who left the hospital before cure was accomplished fared less well eventually.

Enforced bed rest admittedly may be difficult especially in younger patients but if a complete recovery is to be accomplished this form of therapy cannot be emphasized too strongly. After one month if hypertension, edema and azotemia have subsided and the urine cleared quite well a patient may be allowed bathroom and armchair privileges. If after 4 or 5 months a patient is cured except for urinary changes further enforced rest seems futile for the patient may be considered to have an unhealed case

a diet having a low protein content. From the experimental work of Addis, Farr and Smadel and Chanutin and Ferris it is agreed that an injured kidney heals much faster when a low protein diet is given. As I have pointed out elsewhere a moderately high protein diet not only fails to correct the hypoproteinemia but it actually causes

make "bigger and better kidneys" but the patient dies in uremia.

Generally speaking a diet containing 0.50 to 1.0 gm of protein per kilogram of body weight represents the optimal diet for the nephritic since it fulfills protein requirements adequately and still does not retard healing of the kidney. Vitamin supplements in these diets especially A and D are recommended not only because of added nutritional value but also because they elevate the resistance of the patient's upper respiratory tract to infections which so often lead to renal inflammatory lesions. Vitamins A and D may be given in the form of cod or halibut liver oil capsules. B complex in brewers yeast supplemented by intramuscular injections of thiamine chloride 2 to 3 cc. daily. Vitamin C may be given in tablet form. Iron in the form of iron ammonium citrate 10 grains (0.66 gm) three times daily may

it is felt that patients progressed as satisfactorily on one diet as on the other as these diets did not seem to retard or augment the healing of the renal lesion.

Salt and fluid intake is another problem in the treatment of the acute nephritic and while the exact nature of the effect of salt on the kidney is still questioned it is generally believed that salt does add work for the kidney. The amount of fluid that should be given a patient as has been pointed out above varies with the degree of renal insufficiency. However it is felt that the administration of large quantities of fluid has no adverse effect on the kidney. It is my practice to reduce the sodium chloride to 10 to 20 gm a day. This may be reduced to 10 gm daily if edema persists.

Most authorities advocate the removal of infection such as diseased tonsils, foci of infection in sinuses or apical abscesses about one month after the acute episode. While statistics may fail to provide evidence of the benefit of such removal the individual patient often shows striking benefit.

The surgical treatment of nephritis i.e. decapsulation of a kidney in the treatment

of anuria, has proved beneficial in certain select cases of acute anuria. Decapsulation is based on the theory that the resulting decapsulation of the kidney allows a greater blood flow. Most reports have not shown gratifying results from this method of treatment. I believe this procedure is indicated when there is an anuria lasting for 7 days or more which has resisted the simpler therapeutic measures.

FRANCIS D MURPHY

SUBACUTE GLOMERULONEPHRITIS

Subacute glomerulonephritis may be called a second or later stage of unhealed acute glomerulonephritis with a progressive downward course and ending fatally after a short stormy period. Treatment, to a large extent, is the same in subacute nephritis as in the acute form.

The primary aim is to promote a diuresis. This is accomplished by giving an adequate amount of fluid, preferably a milder alkaline one. Sometimes theobromine or some other xanthine 10 grains (0.6 gm.), may be given two or three times daily. Salyrgan, novasurol and any of the mercurial diuretics are contra-indicated. Magnesium sulfate or any of the saline cathartics may prove beneficial though at times there is such an outpouring of fluid into the pleural, pericardial, or peritoneal sac that repeated tapping is necessary to remove it from the cavities.

As in the treatment of the acute phase, a high caloric diet with a moderate amount of protein is indicated as well as iron tonics such as iron and ammonium citrate, 15 grains (1 gm.), three times daily or tincture of nuxvomica 10 minims (0.6 cc.), three times daily. Fluid and salt limitations to about 1200 cc. a day seem effective in controlling the edema in this form of nephritis.

FRANCIS D MURPHY

THE NEPHROTIC SYNDROME

The term "nephrotic syndrome" is used to designate a clinical condition which occurs in its purest form in genuine lipid nephrosis and in certain types of chronic glomerulonephritis in which the tubular system is predominantly involved. A combination of factors which produces the characteristic

clinical picture of the nephrotic syndrome

sense are hypertension, hematuria, azotemia, and uremia.

Depending on the nature of the basic renal disease the main features of the nephrotic syndrome vary in degree as, for example, in genuine lipid nephrosis the heavy albuminuria, excessive edema, marked lowering of the plasma albumin, and a decided hyper

drome the degree of edema, albuminuria, and other features may vary considerably.

In the treatment of the nephrotic syndrome it makes a difference if the glomeruli of the kidney are extensively disordered or if the tubules are badly damaged with the glomeruli slightly involved. This is particularly true when a high protein diet is considered for the treatment of the hypoalbuminemia. When the glomeruli are badly damaged it is a dangerous thing to give a high protein diet because this leads to further glomerular breakdown. Hypertension, hematuria and azotemia are the chief manifestations of glomerular activity. However, with the glomeruli practically intact, a high protein diet does no damage to the disordered tubules.

It is the control of the edema which occupies the chief attention in the treatment of the nephrotic syndrome. This however de

pendent on the adequate control of sodium in the diet and the proper use of fluids. The hypercholesterolemia and the doubly refracting lipoids in the urine require no special treatment as they tend to disappear when the other factors are controlled.

One of the characteristic manifestations of the nephrotic syndrome is the continuous loss of large amounts of protein in the urine, and a high protein diet is believed to lead to some diuresis by reason of the increased urea that is formed (Christian). Protein intake, therefore, should be as high as is indicated for the individual patient. For the

patient with chronic nephritis, 0.75 gm to 1.0 gm per kilogram of body weight seems to be the optimal amount of protein intake. If the nephrotic syndrome occurs with a minimal amount of glomerular damage, the protein intake may be augmented to 1.5 to 2.0 gm per kilogram of body weight or higher if the patient tolerates it. Epstein was one of the first to advocate a high protein diet to replenish the plasma protein which had become reduced from albuminuria, and at the present time a diet of approximately 1.0 gm of protein per kilogram of body weight per day is considered an optimal amount to be given a patient. If the non-protein nitrogen of the blood rises, a reasonable restriction may become necessary. If the nitrogen equilibrium is not maintained, however, malnutrition, anemia, and cachexia are clinical features that may develop. Blood transfusions until the blood is normal or nearly normal have been tried, and it has been proved that they are of little benefit and may be dangerous if acidosis is severe (Salvesen). Farrar et al. have recommended an acid-ash high protein low sodium diet which is excellent for patients with the nephrotic syndrome. Initially, they point out that six small feedings daily will supply a patient with about 60 gm of protein. Each feeding is composed of one cup of milk and one egg or two slices of bread or one cup of cereal with butter, sugar, spices and flavoring as desired. The next stage of the diet (90 to 130 gm of protein daily) consists of three to six meals providing at least two or three eggs, $\frac{1}{4}$ or $\frac{1}{2}$ pound of meat, fish, or fowl, and six slices of bread or servings of cereal. Not more than two cups of milk, one cup of vegetables, and one cup of fruit is indicated, while sugar, butter, gelatin, prunes, plums and cranberries may be eaten as desired. The foods and foodstuffs to be avoided are the following: salt, soda, salted butter, salt bread or salted meat cheese (except cottage), lima beans, spinach, dates and raisins. A special liquid diet designed to supply a liberal protein, high calorie, and low sodium diet has been described by Spence and Sutton, for it has been their experience that normal diets may prove difficult to administer by the usual methods, particularly during the edematous phase of the disease.

Human albumin, in preference to human pooled plasma which contains a considerable amount of salt, has been determined as a nearly ideal diuretic agent for patients having the nephrotic syndrome associated with a low colloid osmotic pressure due to reduced serum albumin. At the present time, however, the only limiting factor is its expense. The optimal amount of human albumin for a patient per day is 30 to 60 gm given intravenously.

Amino acid therapy has been used in malnutrition as a source of improving serum albumin levels and to induce a positive nitrogen balance. However, there is some evidence to show that serum albumin is a more effective way of satisfying the nitrogen deficit. Amino acids can be prepared in pure crystalline form, although the expense incurred limits their use to special studies. Preparations containing amino acids are now being manufactured in pure enough form to be given parenterally, however, to maintain plasma protein and nitrogen levels. Protein hydrolysate, 50 to 100 gm, may be given orally or intravenously daily. For intravenous injection 5 per cent solution in 5 per cent dextrose in distilled water at a rate of 5 to 20 gm of amino acids per hour is given (Farrar et al.). Thus far amino acid therapy has some distinct disadvantages. Orally it is unpalatable, and for any administration has a relatively high sodium content. There has been no conclusive evidence to show that oral administration of protein hydrolysates is more effective than oral administration of formed proteins.

Acacia, in doses of 500 cc of 1 per cent acacia and 0.06 per cent sodium chloride in distilled water given intravenously, alternating with intravenous doses of 2 cc of mercurhydride every other day, has also been used to bring up the colloidal pressure. If injected slowly, it disappears slowly from the blood, has a replacement value for the hypoproteinemia and causes only slight or no reactions. Unfavorable aspects such as deposition and irritation of the liver and to a less extent the spleen and kidney, however, have been known to occur and have caused its use to be limited. Smalley et al., after experimentally administering large amounts of acacia to dogs and subsequently observing the liver, spleen, and kidneys, found the

liver enlarged, vacuolation of the cells, and varying amounts of acacia present in the organs but no evidence of important damage. They conclude that acacia is not contra-indicated in the therapy of the nephrotic syndrome. Gelatin and globin 25 to 50 gm per day have been used in the same way as acacia, are inexpensive, and seem to be of some value.

While formerly water and salt restriction were of primary concern in managing patients with edema, at present it is only salt which is eliminated from the diets while

the patient has no edema; however, there is no real need for restricting salt to completely, and probably 2 to 3 gm a day would be an optimal amount.

One of the things to remember in the treatment of the nephrotic syndrome is that its presence does not necessarily require the restriction of fluid. Restriction may cut down the excretion of nitrogen and augment chances of uremia while the administration of fairly large quantities of water may act as a diuretic influence and improve the output of nitrogenous substances. There is more than one opinion concerning the optimal amount of fluid to be given to these patients. Some believe that the fluid should be restricted; others that there should be a normal or optimal amount of 1500 to 3000 cc per day, and finally, there are those who think that over 4000 cc a day may be given with benefit. The best course to follow is to give an optimal amount (2500 cc) of fluid a day, and if diuresis does not occur satisfactorily the fluid may be increased. Christian believes that about 1000 to 1200 cc of fluid should be given daily unless this leaves the patient uncomfortably thirsty. If so fluids need to be increased. He also advocates the use of parenteral fluids in the form of 1/2 to 10 per cent aqueous glucose solution but not glucose in normal saline when fluid loss is caused by diarrhea or vomiting. Basically, the output of urine is the kidney's primary function, and an adequate fluid intake is one of our best assurances that an adequate output of urine and the toxic substances of metabolism will be preserved.

Diuretic drugs such as the mercurials,

thimerin, urea, and the acid forming salts, often may cause a marked diuresis, weight fall and decreased edema, but these drugs are to be used reluctantly as they may be more detrimental than beneficial. Many authors have challenged the use of diuretics because of the damage they may inflict on the renal tubules, but it is felt that in cardiac edema where the kidney is swollen and congested the mercurials often may aid in clearing up an already present albuminuria. In renal edema, however, diuretics should be used reluctantly and only when all other measures have failed.

Of the mercurial diuretics, mercupurin, mercurhydrin, and mercurphylline are the most satisfactory and may be given intravenously 2 cc every 1/2 or 4 days orally in suppository form for rectal use only or intramuscularly (thimerin is given subcutaneously). Serious toxic manifestations such as stomatitis, colitis, hematuria, or circulatory collapse are rare unless circulatory failure or nitrogen retention exists. Digitalis may prove beneficial and even a lifesaving measure at this time for patients with cardiac edema, although digitalis used in patients with renal edema is of no value as a diuretic agent.

Determinations of the blood urea nitrogen should also be done during its use. This preparation is contraindicated when azotemia is present.

The acid producing salt ammonium chlor

pointed out that after absorption the ammonia (NH_3) radical becomes involved in

the excessive chloride ion by the kidney requires the excretion of sodium. When the sodium is lost a certain ratio of water is also carried off. It must be remembered that the kidney has a defense mechanism which limits the effect of ammonium chloride. If one gives 10 gm of ammonium chloride a day, on the first day sodium is lost. The

patient with chronic nephritis, 0.75 gm to 1.0 gm per kilogram of body weight seems to be the optimal amount of protein intake. If the nephrotic syndrome occurs with a minimal amount of glomerular damage, the protein intake may be augmented to 1.5 to 2.0 gm per kilogram of body weight or higher if the patient tolerates it. Epstein was one of the first to advocate a high protein diet to replenish the plasma protein which had become reduced from albuminuria, and at the present time a diet of approximately 1.0 gm of protein per kilogram of body weight per day is considered an optimal amount to be given a patient. If the non-protein nitrogen of the blood rises a reasonable restriction may become necessary. If the nitrogen equilibrium is not maintained, however, malnutrition, anemia, and cachexia are clinical features that may develop. Blood transfusions until the blood is normal or nearly normal have been tried, and it has been proved that they are of little benefit and may be dangerous if acidosis is severe (Salvesen). Farrar et al have recommended an acid-ash high protein low sodium diet which is excellent for patients with the nephrotic syndrome. Initially, they point out that six small feedings daily will supply a patient with about 60 gm of protein. Each feeding is composed of one cup of milk and one egg or two slices of bread or one cup of cereal with butter, sugar, spices, and flavoring as desired. The next stage of the diet (90 to 130 gm of protein daily) consists of three to six meals providing at least two or three eggs, $\frac{1}{4}$ or $\frac{1}{2}$ pound of meat, fish, or fowl, and six slices of bread or servings of cereal. Not more than two cups of milk, one cup of vegetables, and one cup of fruit is indicated, while sugar, butter, gelatin, prunes, plums, and cranberries may be eaten as desired. The foods and foodstuffs to be avoided are the following: salt, soda, salted butter, salt bread, or salted meat, cheese (except cottage), lima beans, spinach, dates, and raisins. A special liquid diet designed to supply a liberal protein, high calorie, and low sodium diet has been described by Spence and Sutton for it has been their experience that normal diets may prove difficult to administer by the usual methods, particularly during the edematous phase of the disease.

Human albumin, in preference to human pooled plasma which contains a considerable amount of salt, has been determined as a nearly ideal diuretic agent for patients having the nephrotic syndrome associated with a low colloid osmotic pressure due to reduced serum albumin. At the present time however, the only limiting factor is its expense. The optimal amount of human albumin for a patient per day is 30 to 60 gm. given intravenously.

Amino acid therapy has been used in malnutrition as a source of improving serum albumin levels and to induce a positive nitrogen balance. However, there is some evidence to show that serum albumin is a more effective way of satisfying the nitrogen deficit. Amino acids can be prepared in pure crystalline form although the expense incurred limits their use to special studies. Preparations containing amino acids are now being manufactured in pure enough form to be given parenterally, however, to maintain plasma protein and nitrogen levels. Protein hydrolysate, 50 to 100 gm, may be given orally or intravenously daily. For intravenous injection a 5 per cent solution in 5 per cent dextrose in distilled water at a rate of 5 to 20 gm of amino acids per hour is given (Farrar et al). Thus far amino acid therapy has some distinct disadvantages. Orally it is unpalatable, and for any administration has a relatively high sodium content. There has been no conclusive evidence to show that oral administration of protein hydrolysates is more effective than oral administration of formed proteins.

Acacia, in doses of 500 cc of 6 per cent acacia and 0.06 per cent sodium chloride in distilled water given intravenously, alternating with intravenous doses of 2 cc. of mercurydion every other day, has also been used to bring up the colloidal pressure. If injected slowly, it disappears slowly from the blood, has a replacement value for the hypoproteinemia, and causes only slight or no reactions. Unfavorable aspects such as deposition and irritation of the liver and to a less extent the spleen and kidney, however have been known to occur and have caused its use to be limited. Smalley et al., after experimentally administering large amounts of acacia to dogs and subsequently observing the liver, spleen, and kidneys, found the

er enlarged, vacuolation of the cells, and varying amounts of acacia present in the casts but no evidence of important damage. They conclude that acacia is not contraindicated in the therapy of the nephrotic syndrome. Gelatin and globin, 25 to 50 gm per day, have been used in the same way as acacia, are inexpensive, and seem to be of some value.

While formerly water and salt restriction was of primary concern in managing patients with edema at present it is only salt which is eliminated from the diets while

patient has no edema, however, there is a real need for restricting salt so completely, and probably 2 to 3 gm a day would be an optimal amount.

One of the things to remember in the treatment of the nephrotic syndrome is that presence does not necessarily require the restriction of fluid. Restriction may cut down the excretion of nitrogen and augment the excretion of uremia while the administration of fairly large quantities of water may act as a diuretic influence and improve the output of nitrogenous substances. There is more than

amount
Some
noted,

others that there should be a normal or optimal amount of 1500 to 3000 cc per day, and finally, there are those who think that over 4000 cc a day may be given with bene-

The best course to follow is to give an optimal amount (2500 cc) of fluid a day, and if diuresis does not occur satisfactorily the fluid may be increased. Christian believes that about 1000 to 1200 cc of fluid should be given daily unless this leaves the patient uncomfortably thirsty. If so fluids need to be increased. He also advocates the use of intravenous fluids in the form of 5 to 10 per cent aqueous glucose solution but not glucose in normal saline when fluid loss is caused by diarrhea or vomiting. Basically, the output of urine is the kidney's primary function and an adequate fluid intake is one of our first assurances that an adequate output of urine and the toxic substances of metabolism will be preserved.

Diuretic drugs, such as the mercurials,

thimerin, urea and the acid forming salts, often may cause a marked diuresis weight fall, and decreased edema, but these drugs are to be used reluctantly as they may be more detrimental than beneficial. Many authors have challenged the use of diuretics because of the damage they may inflict on the renal tubules, but it is felt that in cardiac edema where the kidney is swollen and congested the mercurials often may aid in clearing up an already present albuminuria. In renal edema, however, diuretics should be used reluctantly and only when all other measures have failed.

Of the mercurial diuretics, mercupurin, mercurhydrin and mercuraphylline are the most satisfactory and may be given intravenously 2 cc every 3 or 4 days orally, in suppository form for rectal use only, or intramuscularly (thimerin is given subcutaneously). Serious toxic manifestations such as stomatitis, colitis, hematuria, or circulatory collapse are rare unless circulatory fail-

edema although digitalis used in patients with renal edema is of no value as a diuretic agent.

Urea in large amounts, 15 gm two to five times daily in fruit juices or syrup of acacia may be given for 1 to 3 weeks. Weekly determinations of the blood urea nitrogen should also be done during its use. This preparation is contraindicated when azotemia is present.

The acid producing salt, ammonium chlo-

pointed out that after absorption, the ammonium (NH_4) radical becomes involved in the general nitrogen metabolism.

patient has received this. The excretion of the excessive chloride ion by the kidney requires the excretion of sodium. When the sodium is lost, a certain ratio of water is also carried off. It must be remembered that the kidney has a defense mechanism which limits the effect of ammonium chloride. If one gives 10 gm of ammonium chloride a day, on the first day sodium is lost. The

patient with chronic nephritis, 0.75 gm to 1.0 gm per kilogram of body weight seems to be the optimal amount of protein intake. If the nephrotic syndrome occurs with a minimal amount of glomerular damage, the protein intake may be augmented to 1.5 to 2.0 gm per kilogram of body weight or higher if the patient tolerates it. Epstein was one of the first to advocate a high protein diet to replenish the plasma protein which had become reduced from albuminuria and at the present time a diet of approximately 1.0 gm of protein per kilogram of body weight per day is considered an optimal amount to be given a patient. If the non-protein nitrogen of the blood rises a reasonable restriction may become necessary. If the nitrogen equilibrium is not maintained, however, malnutrition, anemia and cachexia are clinical features that may develop. Blood transfusions until the blood is normal or nearly normal have been tried, and it has been proved that they are of little benefit and may be dangerous if acidosis is severe (Salvesen). Farrar et al. have recommended an acid ash high protein low sodium diet which is excellent for patients with the nephrotic syndrome. Initially they point out that six small feedings daily will supply a patient with about 60 gm of protein. Each feeding is composed of one cup of milk and one egg or two slices of bread or one cup of cereal with butter, sugar, spices, and flavoring as desired. The next stage of the diet (90 to 130 gm of protein daily) consists of three to six meals providing at least two or three eggs, $\frac{1}{4}$ or $\frac{1}{2}$ pound of meat fish, or poultry and six slices of bread or servings of cereal. Not more than two cups of milk, one cup of vegetables, and one cup of fruit is indicated, while sugar, butter, gelatin, prunes, plums and cranberries may be eaten as desired. The foods and foodstuffs to be avoided are the following: salt, soda, salted butter, salt bread, or salted meat, cheese (except cottage), lima beans, spinach, dates and raisins. A special liquid diet designed to supply a liberal protein high caloric, and low sodium diet has been described by Penning and Sutton for it has been their experience that normal diets may prove difficult to administer by the usual methods, particularly during the edematous phase of the disease.

Human albumin, in preference to human pooled plasma which contains a considerable amount of salt has been determined as a nearly ideal diuretic agent for patients having the nephrotic syndrome associated with a low colloid osmotic pressure due to reduced serum albumin. At the present time however, the only limiting factor is its expense. The optimal amount of human albumin for a patient per day is 30 to 60 gm given intravenously.

Amino acid therapy has been used in malnutrition as a source of improving serum albumin levels and to induce a positive nitrogen balance. However, there is some evidence to show that serum albumin is a more effective way of satisfying the nitrogen deficit. Amino acids can be prepared in pure crystalline form, although the expense incurred limits their use to special studies. Preparations containing amino acids are now being manufactured in pure enough form to be given parenterally, however, to maintain plasma protein and nitrogen levels. Protein hydrolysate, 50 to 100 gm, may be given orally or intravenously daily. For intravenous injection 5 per cent solution in 5 per cent dextrose in distilled water at a rate of 5 to 20 gm of amino acids per hour is given (Farrar et al.). Thus far amino acid therapy has some distinct disadvantages. Orally it is unpalatable, and for any administration has a relatively high sodium content. There has been no conclusive evidence to show that oral administration of protein hydrolysates is more effective than oral administration of formed proteins.

Acacia, in doses of 500 cc of 1 per cent acacia and 0.06 per cent sodium chloride in distilled water given intravenously, alternating with intravenous doses of 2 cc of mercurhydram every other day, has also been used to bring up the colloidal pressure. If injected slowly, it disappears slowly from the blood, has a replacement value for the hypoproteinemias, and causes only slight or no reactions. Unfavorable aspects such as deposition and irritation of the liver and to

experimentally administering large amounts of acacia to dogs and subsequently observing the liver, spleen, and kidneys, found the

liver enlarged, vacuolation of the cells, and varying amounts of acacia present in the organs but no evidence of important damage. They conclude that acacia is not contraindicated in the therapy of the nephrotic syndrome. Gelatin and globin 25 to 50 gm per day, have been used in the same way as acacia are inexpensive, and seem to be of some value.

While formerly water and salt restriction were of primary concern in managing patients with edema, at present it is only salt which is eliminated from the diets while

the patient has no edema, however, there is no real need for restricting salt so completely, and probably 2 to 3 gm a day would be an optimal amount.

One of the things to remember in the treatment of the nephrotic syndrome is that its presence does not necessarily require the restriction of fluid. Restriction may cut down the excretion of nitrogen and augment chances of uremia while the administration of fairly large quantities of water may act as a diuretic influence and improve the output of nitrogenous substances. There is more than one opinion concerning the optimal amount of fluid to be given to these patients. Some believe that the fluid should be restricted, others that there should be a normal or optimal amount of 1500 to 3000 cc per day, and finally, there are those who think that over 4000 cc a day may be given with benefit. The best course to follow is to give an optimal amount (2500 cc) of fluid a day, and if diuresis does not occur satisfactorily the fluid may be increased. Christian believes that about 1000 to 1200 cc of fluid should be given daily unless this leaves the patient uncomfortably thirsty. If so fluids need to be increased. He also advocates the use of parenteral fluids in the form of 5 to 10 per cent aqueous glucose solution but not glucose in normal saline when fluid loss is caused by diarrhea or vomiting. Basically, the output of urine is the kidney's primary function and an adequate fluid intake is one of our best assurances that an adequate output of urine and the toxic substances of metabolism will be preserved.

Diuretic drugs, such as the mercurials,

thiomerin, urea, and the acid forming salts, often may cause a marked diuresis, weight fall, and decreased edema, but these drugs are to be used reluctantly as they may be more detrimental than beneficial. Many authors have challenged the use of diuretics because of the damage they may inflict on the renal tubules, but it is felt that in cardiac edema where the kidney is swollen and con-

used reluctantly and only when all other measures have failed.

Of the mercurial diuretics mercurpurin, mercurhydrin, and mercurphylline are the most satisfactory and may be given intravenously 2 cc every 3 or 4 days, orally, in suppository form for rectal use only, or intramuscularly (thiomerin is given subcutaneously). Serious toxic manifestations such as stomatitis, colitis, hematuria or circulatory collapse are rare unless circulatory fail-

edema, although digitals used in patients with renal edema is of no value as a diuretic agent.

Urea in large amounts, 15 gm two to five times daily, in fruit juices or syrup of acacia may be given for 1 to 3 weeks. Weekly determinations of the blood urea nitrogen should also be done during its use. This preparation is contraindicated when azotemia is present.

The acid producing salt, ammonium chloride is given in enteric coated tablets in an average dose of 10 to 30 gm per day. In a recent therapeutic conference Marshall has pointed out that after absorption, the ammonia (NH_3) radical becomes involved in the general nitrogen metabolism of the body and disappears from the blood, leaving the chloride ion remaining. Thus in effect the patient has received HCl. The excretion of the excessive chloride ion by the kidney requires the excretion of sodium. When the sodium is lost a certain ratio of water is also carried off. It must be remembered that the kidney has a defense mechanism which limits the effect of ammonium chloride. If one gives 10 gm of ammonium chloride a day, on the first day sodium is lost. The

second day loss is not large the third day, sodium excretion will be normal. We know that the mechanism of the kidney for producing ammonia is sluggish. The production of ammonia the first day is slow but rises gradually to its peak on the fourth day. As the ammonia continues to be produced the elimination of sodium is less. Therefore in the use of ammonium chloride large doses are more effective than small doses and large doses should be given for the first 3 or 4 days and then stopped. When the kidney is damaged it may be dangerous to give the acid producing salts because in advanced nephritis for example ability to form am-

present. Caution must be exercised therefore in using these acid producing salts in the presence of a damaged kidney. Christian has mentioned that the ammonium salts seem to produce a minimum of gastro intestinal

little harm and disappears with discontinuance of the drug.

Potassium nitrate or potassium chloride has also been used in a similar fashion as ammonium chloride or ammonium nitrate. However while patients receiving ammonium salts are guarded clinically against acidosis those receiving potassium salts should be watched for arrhythmias.

Dried thyroid in 0.06 gm dosage daily and increased at weekly intervals is considered in the treatment of the nephrotic syndrome by many investigators as the basal metabolic rate is decreased in many patients having this condition. However, it is my opinion that no benefits follow giving thyroid and in many instances thyroid intoxication, nervousness or tachycardia may be the end result.

In the treatment of the nephrotic syndrome the control of infection is an important consideration as in the past patients with this disorder died not of nephrosis nor of

been a common cause of death in these cases. With the advent of the antibiotics this complication has been found to be more easily controlled.

In certain cases of nephrosis a condition known as "nephrotic crisis" may develop. This is said to occur when the plasma amino acid nitrogen concentration drops below a

erysipelas which involves the edematous swollen tissues of the body. Sometimes pneumonia, peritonitis or pleuritis may develop. Usually the pneumococcus is the offending organism but the staphylococcus may also occur. The exact cause and nature of nephrotic crisis is unknown.

The intravenous injection of 5 per cent amino acid solution in 5 per cent glucose solution is indicated several times daily in the treatment of this disorder. Some believe that regular administrations of solutions of amino acids are indicated in order to prevent the onset of these episodes. For the fever and the infection penicillin in adequate doses of about 1,000,000 units a day provides gratifying results.*

FRANCIS D MURPHY

CHRONIC GLOMERULONEPHRITIS

In the treatment of chronic nephritis there are two important factors which are closely related but for practical purposes may be considered separately: (1) the kidney lesion itself; (2) the numerous clinical manifestations which are the result of the alterations in the physicochemical balance of the body due to renal insufficiency. Although the correlation between these two is poorly understood treatment is fairly satisfactory.

It is the fact that certain observations presented are of an experimental nature.—Ed for

Farnsworth E B Studies on the Influence of

Ammonium Chloride in Simple

It is the control of the various imbalances of fluid electrolyte protein metabolism resulting from the kidney disease that is the chief object of treatment. In addition it must be remembered that a patient having chronic nephritis may have a diminished kidney function due to gastro intestinal disturbances cardiovascular disorders cerebral conditions or general malnutrition. These symptoms therefore should be considered more seriously in the general management of chronic nephritis and adequate quantities of food sufficient rest and recreation and the removal of any foci of infection which are indicated.

Treatment of the Kidney Lesion Itself
The treatment of the kidney lesion itself depends a good deal on the nature and the extent of the involvement of the structures of the kidney. For example there may be extensive glomerular damage with minimal involvement of the tubules which leads to a clinical picture of hypertension hematuria and azotemia or there may be a minimal glomerular involvement with extensive tubular damage which produces a picture of extensive albuminuria edema and hypercholesterolemia and little or no hypertension hematuria or azotemia. The combination present decides to a large extent the exact nature of treatment.

In the treatment of the renal lesion itself there are three important factors to be considered: rest, diet and special drugs and therapeutic agents. In these cases as in therapeutics in general rest is most important. It is difficult to outline precisely the nature of rest necessary in chronic nephritis. In certain other diseases such as angina pectoris and coronary insufficiency the pain is used as the guidepost for rest and relaxation but in kidney disease there is no pain and therefore it is hard to make an exact rule. Rest to the kidney may be obtained in a direct way by keeping the patient at a minimal amount of physical activity and reducing his weight by proper dietary measures. Obviously the amount of rest to be prescribed depends on how far the chronic nephritis has advanced.

In the earlier stages a 50 per cent reduction in the patient's physical activity is probably all that is necessary. Later when renal function has become badly impaired the

patient may be restricted to bed with only bathroom and armchair privileges. The reduction of physical activity of course diminishes the metabolic requirements of the body and therefore reduces work for the kidney.

Many observers believe that chronic nephritis may develop when patients with unhealed acute nephritis are fed a high protein diet. On the other hand there are those who have proved that a high protein diet is not harmful to a patient with chronic nephritis. It must be emphasized again that a patient with this form of renal disease may be in a debilitated condition and by restricting protein in the diet his nutrition may be further impoverished. Therefore while it is difficult to lay down a rule of individual food requirements since food regulation varies with the various stages and forms of the disease nevertheless it is an accepted fact that management of the condition is centered around the protein salt and fluids of the diet. In addition alcoholic beverages and tobacco should be restricted in most cases as they are usually harmful and the patient feels better when they are not used.

The protein of the diet should be kept at a low level as it is generally accepted that an excessive amount of protein in the diet retards healing and makes the kidney disease worse. What constitutes an optimal protein intake varies with different writers. It is generally accepted now that 0.5 to 0.75 gm per kilogram of body weight is an acceptable figure.

Sodium in the diet should not exceed more than 1.0 gm a day as there is an excessive amount of sodium chloride in the tissues. Some of these therapeutic measures have been discussed previously under treatment of the nephrotic syndrome.

As in protein regulation the fluid requirement in chronic glomerulonephritis varies greatly. At the present time it is the consensus that about 1200 to 1800 cc of fluid is a moderate intake. If the patient is sweat

limited to from 800 to 1200 cc daily unless the kidney fails to excrete nitrogen or the renal function tests point to advanced functional impairment at which time

should be pushed. In the presence of hypertension fluids should be restricted if there is no renal insufficiency. After a period of actual measuring of the fluid intake, the patient's thirst is a natural guide to the amount of fluid given.

Many standard nephritic diets have been used. Usually the protein is

Breakfast	Fruit—fresh stewed or dried cereal	$\frac{1}{2}$ cup
	Cereal	$\frac{1}{2}$ cup cooked or $\frac{1}{4}$ cup dry cereal
	Milk	$\frac{1}{2}$ cup
	Bread or toast	2 slices with $1\frac{1}{2}$ sq. butter
	Cream	$\frac{1}{4}$ cup
	Postum or kaffee Hag	1 cup
Dinner	Meat—liver beef lamb mutton fowl fresh fish	1 slice $\frac{1}{4}$ " thick
	Potato rice or macaroni	$\frac{1}{2}$ cup
	Vegetable	$\frac{1}{2}$ cup
	Bread	1 slice with 1 sq. butter
	Simple dessert—tapioca cornstarch pudding plain icecream custard etc.	$\frac{1}{4}$ cup
	Milk	$\frac{1}{2}$ cup
	Water	1 cup
2:30 P.M.	Water lemonade or orangeade	1 cup
Supper	Milk or	
	Cream soup (made without meat or meat stock)	1 cup
	Potato rice or macaroni prepared with milk cheese or egg	$\frac{1}{2}$ cup
	Vegetable	$\frac{1}{2}$ cup
	Salad preferably made with fresh vegetable	$\frac{1}{2}$ cup
	Bread	1 slice with 1 sq. butter
	Fruit	$\frac{1}{2}$ cup
8:00 P.M.	Water orangeade lemonade	1 cup

Use no table salt and none in cooking unless prescribed by doctor

1 cup means 1 MEASURING cup

Occasionally substitute 1 cup of Ovaltine or cocoa for 1 cup of milk

Only fresh fruit may be eaten between meals

OMIT FROM THE DIET

Salted meats

Bacon
Smoked ham
Corned beef
Salted fish
Meat soups or
Meat broths

Highly seasoned foods

Pepper
Vinegar
Spices
Pickles
Catsup

Miscellaneous

Tea
Coffee
Rich gravies
Rich pastries

Use peas baked beans lima beans and soy beans only occasionally

There are special dietary measures to be used especially when the kidney is failing to excrete the nitrogenous substances adequately. In the more advanced cases of chronic nephritis especially with nitrogen retention and hypertension the diet suggested by Kempner may be used. This diet provides an average intake of 250 to 350 gm of rice (dry weight) daily, which is either boiled or steamed in plain water, and fruit juice, without salt milk or fat.

Iron therapy has been a standby in the

treatment of chronic nephritis as anemia is frequently present. Iron and ammonium citrate 10 grains (0.6 gm) three or four times a day has been a favorite for many years. Vitamins occupy a questionable therapeutic position but as the general nutrition of the patient is usually undermined by nephritis, some form of multiple vitamin therapy may be helpful.

Regarding the treatment of the renal lesion itself, removal of a focus of infection must occupy a prominent place. Diseased tonsils

infected sinuses and infected teeth may be the source of an infection which retards the healing process in the kidney. Although once it sets in chronic nephritis rarely if ever heals completely it is important to remember that the course of chronic nephritis is characterized by periods of remissions and periods of activity. It is the function of the physician in charge to bring about a remission in the inflammatory lesion of the kidney and to maintain this remission as long as is possible by exercising good clinical judgment and employing all the therapeutic measures at hand.

Treatment of the Clinical Manifestations. As a result of chronic glomerulonephritis certain clinical syndromes develop which require special treatment. Chronic nephritis is characterized by the five main syndromes: the urinary syndrome, edema, hypertension, azotemia, and uremia. These syndromes may all occur at the same time and during the course of nephritis one or all of them may disappear for a time, perhaps to return later or never to return. At times in the course of nephritis hypertension and hematuria dominate the picture; at other times edema will be the outstanding feature, and azotemia and uremia usually terminate the course of chronic glomerulonephritis. In

where

Hypertension indicates that the glomeruli of the kidney are involved. A persistent

and the symptoms which attend it occupies an important place in the therapy of nephritis. The general management of the case requires close consideration of the diet, of the weight, and of the general nutrition of the body. There are a few special measures which must be given consideration.

As cardiac embarrassment is a sequel to hypertension, all efforts must be made to protect the heart as fully as possible. This is done by reducing physical and mental ac-

procedure to reserve the use of digitalis until the heart shows evidence of embarrassment by enlargement, dyspnea, or edema. In such cases digitoxin or its equivalent in doses of 0.2 mg. may be given daily or as often as indicated. Special measures such as potassium thiocyanate may be used if there is a severe hypertension and if headaches attend it. However, potassium thiocyanate is a drug which may bring about unfavorable toxic manifestations and it should be used only when other measures fail to bring relief. If it is decided to use potassium thiocyanate 3 grains (0.2 gm.) are given two or three times a day. The administration of this drug must be guided by the level of the potassium thiocyanate in the blood. The optimal level is 8 to 12 mg. per cent and the determinations must be made at weekly or biweekly intervals. When this drug is used it is best to add either rutin 20 mg. three times a day or some preparation of vitamin C in doses of 25 to 50 mg. three times a day. Other drugs have been advocated such as theophylline and other members of the xanthine group.

As chronic glomerulonephritis progresses azotemia or retention of nitrogenous products in the blood stream occurs. The treatment of azotemia is as follows: The fluid intake is increased to 4000 to 5000 cc. a day or enough fluid is given to assure an adequate output of urine for the output of the nitrogenous substances is to a large extent dependent upon the output of urine. Therefore the output of urine becomes one of the most important factors in the treatment of chronic nephritis. The kind of fluid to be

the patient is vomiting and uremia becomes imminent then the question of intravenous fluid administration must be answered. This will be taken up in the section on uremia.

Azotemia depends on the functional capacity of the kidney. The reduction of the protein in the diet to as low as 0.5 gm. per kilogram of body weight not only takes a load off of the kidney itself but retards the development of azotemia.

When azotemia is not corrected the natural sequence of events leads to uremia.

FRANCIS D. MURPHY

UREMIA

Uremia may be divided into two distinct forms although both of them frequently occur together (1) *Genuine uremia* which is the result of any disease which impairs the secretion of urine and leads to retention of the toxic substances of metabolism not only nephritis but obstructive uropathies may be responsible for this kind of uremia (2) *Convulsive uremia* in which convulsive seizures are the chief manifestation This type of uremia has nothing to do with the retention of nonprotein nitrogen but is most likely the result of increased cerebrospinal fluid pressure which in turn results from hypertension

Genuine Uremia Genuine uremia is commonly the result of chronic glomerulonephritis in which the renal parenchyma is almost completely destroyed The clinical features of genuine uremia are practically the same whether the uremia is the result of chronic nephritis polycystic kidney disease tuberculosis of the genito urinary tract or of any other cause As the result of these changes alterations in the chemical composition of the blood may occur and it is the management of these alterations which occupies our main attention in the treatment As the uremic state may develop and occur in various degrees of severity in the course of many disorders the discussion of the treatment must obviously be quite general There are however three principal factors which will receive emphasis here (1) reduction of the intake of protein by which an attempt is made to cut down the work of the kidney (2) the attempts to promote diuresis and thereby augment the output of urine which in turn increases output of nitrogenous substances (3) the control of the electrolyte imbalance and the relief of symptoms

The reduction of the intake of protein is accomplished by giving a diet of 0.5 to 0.6 gm of protein per kilogram of body weight There is not much evidence to believe that there is any significant difference between any of the protein foods whether eggs milk or white or red meat Such low protein diets are usually easy for the patient to follow after they have become accustomed to it although it is well to supplement such low protein diets with the proper minerals and

vitamins necessary for the case The amount of salt that is given in the diet is about 2 gm a day unless edema is present In such cases the sodium intake is reduced further In case the patient is vomiting however there may be hypochloremia and the addition of sodium chloride to the diet makes the diet more palatable and may make the patient feel much better Often in uremia there occurs a phase known as the salt losing stage in which there may be a genuine hypochloremia This must be corrected by the addition of salt to the diet or by the administration of intravenous physiologic saline solution

It is important to increase the output of urine as the output of urea and the other toxic substances of metabolism depend on the urinary output This is accomplished by giving 2000 to 4000 cc of fluid a day unless there is some special contraindication to this amount Heart failure constitutes the main contraindication for large quantities of fluid

In uremia renal insufficiency is usually fairly well advanced and the use of the stronger mercurial diuretics is not indicated However aminophylline or other xanthine diuretics may be tried For example 7½ grains (0.5 gm) of aminophylline may be

salt type and the mercurials are contraindicated as they may promote an already impending acidosis At times the urinary output is dependent on the condition of the heart and the general circulation Small doses of digitalis may be used to improve the circula

In genuine uremia nausea vomiting and acidosis occur These require the use of intravenous solutions for the purpose of combating dehydration acidosis and electrolyte imbalances The question arises as to what kind of fluids and how much is to be given The answer may be stated in a practical way There are four kinds of fluids in common use (1) glucose solutions 5 10 and 50 per cent (2) physiologic salt solution (3) whole blood plasma and serum albumin (4) the alkaline solutions such as sodium bicarbon

ate, 75 per cent solution and $\frac{1}{2}$ molar lactate solution. In order to determine which fluid should be given, certain determinations of the blood must be made. The quantity of blood urea nitrogen is determined as well as the quantity of albumin in the plasma, the CO_2 combining power, and the level of the sodium and chloride of the blood. On these determinations one injects the fluid which is indicated. For example, if there is a rising nonprotein nitrogen in the blood stream, 5 per cent solutions are given in doses of 2000 to 3000 cc a day in order to promote diu-

r
t
t

By determining the CO_2 combining power of the blood the presence of acidosis or alkalosis is decided. In impending acidosis, which is the usual thing in uremia, 1000 cc of 5 per cent sodium bicarbonate may be given every day. The remainder of the fluid requirement is made up by giving 5 or 10 per cent glucose solutions in adequate amounts. By these measures electrolyte and acid base imbalances may be corrected. It is always well to determine the plasma albumin content and if there is a deficiency, plasma albumin may be used to correct it.

Nausea, vomiting, headache, delirium, and coma are common clinical features of uremia. These may become very distressing and require skillful therapeutic management. For the headache, compounds of acetylsalicylic acid, barbiturates, and codeine are usually sufficient. Occasionally it is necessary to resort to pantopon or to morphine. Chloral hydrate may have to be given by rectum, 60 grains (4 gm), in 4 ounces of water. This may be repeated two or three times in a day. For vomiting, sodium pentobarbital, $\frac{1}{2}$ to 1 grains (0.1 to 0.2 gm), or sodium amylal in the same dose may be given. Occasionally venesection of 500 cc of blood may be beneficial especially if the hypertension is present. The fluid may be replaced by physiologic saline or some other fluids. If vomiting persists, a stomach tube may be passed and gastric lavage undertaken with sodium bicarbonate solution.

Within recent years more radical measures than those given above have been brought into use for the treatment of uremia. These measures may be summarized under the

headings of peritoneal dialysis, intestinal lavage, and the use of the artificial kidney. Peritoneal dialysis has recently been reintroduced by Seligman, Frank, and Fine. This kind of treatment, although it is becoming widely accepted and is apparently quite useful, requires the careful consideration of many factors. For example, the electrolyte balance must be precisely controlled and the danger of peritonitis kept in mind at all times. This form of treatment should be reserved for cases of renal insufficiency in which there are good chances of reversing the renal disease in progress. The results of intestinal lavage have not been as satisfactory as those obtained with peritoneal lavage.

There is more than one solution recommended for peritoneal irrigation and they may be enumerated as follows: Tyrode's solution (20 to 30 liters daily) to avoid plasma depletion of electrolytes, glucose to avoid acidosis, penicillin and sodium sulfadiazine to prevent infection, and heparin to inhibit fibrin deposition.

The lavage consists of running in about 5 to 20 liters a day. It is continued steadily if possible for several days or until the condition of the patient is satisfactory.

Convulsive Uremia. Convulsive uremia may occur in conjunction with genuine uremia or it may develop independent of genuine uremia. It is the result not of retention of substances of a nitrogenous nature but is usually produced by hypertension, increased cerebrospinal fluid pressure, and is followed by convulsions. In these cases it is important to control the twitching and convulsions because they may lead to cardiac failure, respiratory failure, or both. Control of the convulsion may be attended by the use of magnesium sulfate. This may be given intravenously, in 15 gram (1 gm), doses three or four times a day. During the use of this substance the blood pressure and the respiratory rate must be watched closely. If the respiratory rate falls to 12 or below per minute, calcium gluconate must be held in readiness and given intravenously in doses of 10 to 20 cc. This offsets the detrimental action of the magnesium. Sometimes it is necessary to sedate the patient by giving pantopon or one of the barbiturates.

topon, $\frac{1}{2}$ grain (0.20 gm), morphine, $\frac{1}{4}$ grain (0.15 gm), with atropine, $\frac{1}{100}$ grain (0.06 gm), may be repeated for the control of the twitching and the convulsion. Chloral hydrate per rectum is an old standby. It is given, 30 to 60 grain (2 to 4 gm), doses rectally, two or three times a day if necessary.

In the past the removal of spinal fluid by spinal puncture has been recommended in these cases. There is some danger, however, in such a procedure because with the release of fluid on the brain the *medulla oblongata* may become jammed in the foramen magnum resulting in respiratory paralysis and death. Within recent years I have not used this measure. The control of the convulsion is exceptionally important in the treatment of nephritis because, unlike genuine uremia, in convulsive uremia the patient may recover from the episode and live fairly comfortably for many years afterward.

Extrarenal Uremia Extrarenal uremia is a condition commonly characterized by elevation of the blood nitrogen, dehydration, hypochloremia, normal or low blood pressure, and oliguria which may progress to anuria. This syndrome usually occurs in association with some primary disorder independent of the kidney or urinary tract, such as intestinal obstruction, excessive vomiting or diarrhea from any cause or any condition causing dehydration and elimination of chlorides from the *gastro intestinal tract*.

In the treatment of extrarenal uremia there are two things to be considered: correction of dehydration and restoration of the volume and electrolyte composition of the blood to normal and treatment of the shock-like condition which has complicated the primary disease under consideration. These conditions must be reversed before anything else is accomplished, although if the primary cause of the condition is known, such as bowel obstruction, it should be corrected as soon as possible.

The fluid-electrolyte-protein composition of the blood is accomplished by the administration of the correct kind of fluid, the proper amount, and the optimal rate of administration. Physiologic saline solution, 3000 to 4000 cc every day, restores the extracellular electrolytes and water. In the presence of acidosis, sodium bicarbonate or sodium lac-

tate intravenously is beneficial, in alkalosis, normal saline or ammonium chloride (200

amino acids, blood plasma, or both are given, although if food is tolerated by the patient, small feedings consisting of liquid or semi-solid carbohydrate food are advisable. If nausea and vomiting persist, nothing should be given by mouth as this serves to accentuate the disorder.

Shock, if present, must be combated, and blood transfusions usually are of value.

FRANCIS D. MURPHY

LIPOID NEPHROSIS

There is no unanimity of opinion regarding the nature of genuine lipid nephrosis. Most observers believe that lipid nephrosis is, in fact, a stage or a phase of chronic glomerulonephritis. Personal observations,

lipid nephrosis is that many, but not all, chronic glomerulonephritis have the nephrotic syndrome which may appear almost identical with the syndrome of genuine lipid nephrosis.

For practical purposes, lipid nephrosis is a disease of the tubular apparatus with little or no inflammatory involvement of the glomeruli. Even though, as Bell emphasizes, most cases of so-called "pure lipid nephrosis" show some degree of glomerulitis, there are many patients with such a minimal glomerular involvement that for all practical purposes it may be considered lipid nephrosis.

In lipid nephrosis there are four outstanding abnormalities: (1) an excessive loss of protein through the kidneys, (2) a reduction of the serum albumin, usually to 2 gm per cent or below, with the consequent reduction of the osmotic pressure (3) the presence of cholesterol crystals in the urine which doubly refract polarized light and gives to the disorder its name and one of its peculiar characteristics.

As the cause of lipoid nephrosis is not known, the treatment must be empirical. There are three therapeutic considerations.

General Care The general care and the protection of the patient from infection, particularly pneumococcal infection which has been a common cause of death in these cases. The patient should obtain almost complete rest, as exercise seems to augment the albuminuria and the edema.

Diet The diet occupies a most important position and is based on the idea that albumin of the blood stream leaks away in the urine. Attempts have been made to replenish the plasma albumin by a high protein diet of between 3 and 4 gm per kilogram of body weight. In addition to this optimal amounts of carbohydrate and fat are also given. Because of the hypercholesterolemia a diet low in cholesterol such as one avoiding eggs is indicated. One of the defects with the high protein diet is that many patients find such a diet obnoxious. Concerning other dietary factors, the sodium of the diet must be kept at a low level. It is best to keep

certain amount of sodium intrinsically. For practical purposes, then, it is best to call for a diet without added salt and request a diet made up of salt free butter and bread and desalted milk.

Whether limitation of fluid is advantageous has not been completely decided. For my own purposes, I allow an optimal amount of fluid a day about 1500 to 2500 cc which satisfies the patient's requirements. Schemm and others use a greater amount of fluid, with an acid ash diet, in an attempt to eliminate the sodium ion as completely as possible. Such a routine as Schemm has recommended has not been completely satisfactory in many cases of nephrosis. However, it deserves further trial before it can be given full approval or condemnation.

The use of intravenous amino acids has been recommended highly by some but my own experience with amino acids intravenously has not been gratifying. Diuretics, such as urea, mercupurin ammonium chloride and the xanthines, have all been tried scores of times and have never found approval. Most of these diuretics may be harm-

less, but the mercurials may be quite detrimental.

Intravenous solutions of human serum albumin are advocated in 25 to 50 gm doses daily until a desired diuresis has occurred. This is the best measure in increasing the colloidal osmotic pressure. The use of other substances for the purpose, such as blood plasma, acacia, gelatin and globin, have their drawbacks. Acacia has been accused of causing enlargement of the spleen and liver and of being more detrimental than beneficial. Many have discontinued its use completely and have condemned it. Globin may be used in 25 to 50 gm doses daily. The reports with globin in lipoid nephrosis have been encouraging.

Removal of Edematous Fluid The question of performing abdominal paracentesis for the ascites of nephrosis is often debated. However, I am in favor of removing the ascites whenever the abdomen becomes tight and respirations are interfered with. To me it always seems to indicate a lack of therapeutic skill when a patient is brought to necropsy with an abdomen distended with fluid and the chest so filled with fluid that the breathing space had been greatly reduced. If abdominal paracentesis is done properly, few or no unfavorable reactions occur. The danger of causing peritonitis in these cases is greatly reduced at the present time by the use of penicillin a day before and a day following the paracentesis.

FRANCIS D. MURPHY

LOWER NEPHRON NEPHROSIS

Lower nephron nephrosis is a disorder which has become widely known within recent years. It is an acute condition characterized by the presence of lipoid vacuolization of the cells lining the ascending limbs of Henle's loop. In the distal convoluted tubules and the collecting tubules, there is precipitation of pigment casts, and these changes are followed by necrosis and extensive degeneration of the epithelial cells of the entire lower nephron. A corresponding clinical picture of severe oliguria or complete anuria, rise in the blood pressure, and an elevation of the nonprotein nitrogen of the blood is present. Nausea, vomiting, weakness, and collapse are also constant fe-

The lower nephron nephrosis may be produced by a variety of disorders. It may occur with the crush syndrome, the transfusion reaction, injuries of various kinds, trauma, abortions, burns, and sulfonamide intoxication as well as many other things. These clinical and pathologic complications give rise to many theoretical considerations in treatment.

At the present time there are many different therapeutic suggestions, but the following treatment seems to be the most practical.

As the chief clinical feature is oliguria or anuria and many of the other changes are dependent on this, immediate treatment is directed to relieving anuria. In this regard, many measures have been advanced, for example, splanchicectomy as recommended by Trueta and associates, spinal anesthesia, roentgen irradiation over the kidneys, and decapsulation. Personal experience with lower nephron disease and anuria prompts me to advocate conservative measures, as follows:

(1) If the patient is in a state of collapse and shock, a transfusion or plasma transfusion must be given to control the shock.

(2) Administration of 1000 to 2000 cc of 5 per cent glucose solution daily is indicated, and if diuresis sets in, the amount of injected fluid may be increased accordingly. If the patient vomits considerably, there may be hypochloremia and if so, a physiologic saline solution may be added to the daily injection of glucose solution.

(3) The CO_2 combining power of the blood is determined as well as the sodium and potassium levels. If there is an acidosis impending, then 5 per cent bicarbonate solutions or $\frac{1}{6}$ molar lactate solutions should be given intravenously to control acidosis. Occasionally alkalosis may be present and if it is, 1000 cc of a 1 per cent ammonium chloride solution may be given to offset the alkalosis.

(4) It is well to determine the plasma albumin content of the blood and add intravenous plasma albumin or plasma to elevate the plasma protein.

(5) As the anuria in these cases is associated with an increased blood volume, careful attention must be given to the heart, for circulatory failure with pulmonary edema may set in and terminate the patient's life. Because of this danger, one must be cautious

of the amount of fluids administered intravenously for, as Strauss points out, many of these patients are drowned with large volumes of intravenous fluids. Early and slow digitalization is indicated in these cases but overdosage must be guarded against.

(6) When diuresis sets in, the amount of intravenous fluids may be increased and the levels of sodium, chloride, potassium, and plasma albumin must be watched closely and proper measures instituted to keep these elements at an optimal level.

Other measures which have been recommended include the intravenous use of 50 cc of 50 per cent glucose with $7\frac{1}{2}$ grains (0.5 gm) of aminophylline, even though diuretics are not particularly advisable in the presence of anuria. Diathermy applied over the kidney area has been followed by fairly satisfactory results in some cases. Decapsulation has been recommended and some good results have been reported. It is not advisable to attempt decapsulation until about the seventh day of anuria, for until this time spontaneous diuresis may occur at any time. Although decapsulation has fallen into disrepute, it is recommended by some urologists.

It is in cases of acute toxic lower nephron nephrosis that the lesion of the kidney is considered to be reversible. Therefore, it is in these cases in which the artificial kidney and peritoneal and intestinal lavage have been advocated. These measures, however, are still in the stage of clinical investigation and are not ready for approval or for recommendation at the present time.

One of the prominent examples of lower nephron nephrosis is brought about by the crush syndrome. This condition may be suspected in a patient with a history of a crushed limb or occlusion of arterial supply for several hours. Upon restoration of the blood flow, the limb usually swells and becomes hard and paralyzed. At times shock occurs which is caused by fall in blood pressure and associated with hemoconcentration. Within the first 24 hours renal damage may not be exhibited, but if it does occur urinary output and specific gravity diminish and unless a large diuresis is established the patient may die from nitrogen and potassium retention.

In treating this condition the following

measures may be instituted (1) pressure bandaging of the injured limb, (2) the use of an alkali for control of an acid urine, (3) restoration of blood volume and blood pressure by controlling shock, (4) adequate fluid intake

The injured limb may be treated by means of a pressure bandage and kept cool to decrease the rate of autolysis and allow living tissue to survive on a smaller blood supply

An alkaline urine may be obtained by giving sodium bicarbonate or some other mild alkali, 60 grains (4 gm) hourly by mouth. If vomiting is present 1 liter of isotonic sodium lactate given intravenously will produce the desired results. If a diuresis cannot be obtained within 12 hours, despite alkali therapy, renal damage should be suspected and fluids and alkaline substances should be stopped as their use may bring about alkalosis which develops readily in patients with renal failure

By the transfusion of plasma and crystalloid solution such as saline or lactate, the fall of renal blood flow may be prevented. Shock may be combated by the usual methods of transfusion of blood and plasma

FRANCIS D. MURPHY

PYELITIS AND PYELONEPHRITIS

Pyogenic infections of the kidney embrace pyelitis, pyelonephritis, pyelonephrosis and infected hydronephrosis conditions that eventually destroy the kidney's function unless the inflammation is controlled. Various organisms may be the cause of these pyogenic infections although *Bacillus coli* is considered the responsible one. *Staphylococcus* or *streptococcus* however, may be the etiologic organism and *Bacillus proteus* may occur on rare occasions. The treatment of these bacterial infections requires a close study of the urologic phases of the disease. One has to determine if obstruction is present and what the nature of the obstruction is before proper treatment can be considered.

No one method of treatment is suitable to every occasion. In some cases the sulfa drugs or the antibiotics will bring about remarkable results while in other cases they may seem to be utterly useless. The main problem in the management of these infec-

tions of the kidney is the elimination of the disorder in its early phase before the disease progresses and leads to total destruction of the renal tissue. The removal of the obstruction and the institution of normal urinary drainage must be carried out by a competent urologist

and there are frequency, urgency, and dysuria. The treatment may be divided into the general and the specific measures.

General treatment consists of rest in bed, administration of large amounts of fluid, 3000 to 4000 cc a day and a carefully selected diet. Furthermore, the dysuria and urgency, which may be intense, are often relieved by giving alkaline drugs as sodium acetate, sodium bicarbonate or sodium citrate. These drugs alkalinize a highly acid urine and bring about relief. Sodium citrate may be given, 60 grains (4 gm) every 24 hours and is safe in such doses even for children.

ment are as follows: (1) the urinary antiseptics, (2) the sulfonamides, (3) penicillin, and (4) streptomycin.

Hexamethylenamine and sodium acid phosphate are excellent urinary antiseptics and may be given in doses of 180 to 225 grains (12.0 to 15.0 gm) three times a day. Antiseptics are useful for a mild pyelitis when the infection is of a low grade and the patient is not particularly ill. The mandelic acid preparations such as ammonium mandelate or calcium mandelate may be given, 30 to 45 gram (2 to 3 gm), doses three or four times every day, i.e., after meals. These antiseptics, however, may cause nausea and

ment of pyogenic kidney conditions for a number of years, and the results have been quite gratifying. Numerous sulfonamide

compounds have been recommended for various kinds of infections of the kidney, but experience within recent years has shown that there is no great difference between various sulfonamides in respect to special action on certain bacteria nor is the reaction of the urine of any great significance in the therapeutics of these drugs.

We must always remember that the sulfonamides may have a toxic action on the kidney. They may cause obstruction in the renal pelvis by the presence of sulfonamide crystals, and thus bring about mechanical disorder in the kidney. However, the sulfonamides may produce a nephrotoxic action on the kidney especially in the tubular apparatus where there may be necrosis and destruction of the epithelial cells of the lower convoluted tubules as well as the cells lining the loops of Henle. Of course, other toxic manifestations occur such as anemia due to hemolysis of the red blood cells, fever and skin eruptions may even produce dermatitis exfoliativa.

The protection of the patient against the toxic reaction of the sulfonamides is accomplished by the use of large quantities of fluids when these compounds are given. It has been shown by Murphy and Woods that the acetate derivatives are more soluble in the alkaline than in the acid urine and it is particularly valuable to keep the urine alkaline when one is administering sulfonamides for the special purpose of preventing renal

in divided doses

Sulfathiazole or sulfadiazine may be used in the same doses, 1 gm every 4 hours. The most popular drug in urinary infections is sulfadiazine, if gram negative organisms are present, however, sulfathiazole is the sulfa drug of choice.

Penicillin is excreted in the urine and is effective in certain types of bacterial infection of the kidney. However, it is considered much less effective than sulfonamides in the treatment of the *Bacillus coli* infections. When the infection is nonhemolytic streptococcal or staphylococcal, the use of penicillin is the therapy of choice, as these coccal infections are resistant to sulfonamides.

The use of penicillin in the treatment of infections of the kidney requires a different standard of dosage than when penicillin is used in generalized septicemia. When a blood culture is positive, the nature and sensitiveness of the organism to penicillin in vitro are of considerable importance in regulating the dosage. The level of penicillin in the blood stream too becomes an important factor in treatment when there is generalized infection. However, in the treatment of urinary tract infections such considerations are not significant. The proper dosage however, is important, and 100,000 units of penicillin intramuscularly every 3 hours will usually bring about gratifying results. If the fever and the infection persist after 3 or 4 days, the dose must be doubled.

Penicillin has not the drawback of the sulfa drugs as toxic reactions are rare. However, they do occur and therefore must be considered. Skin eruptions, rashes and at times even dermatitis exfoliativa may develop. When a skin irritation appears on the face, penicillin should be stopped as it is too dangerous to continue treatment when there is any evidence of intoxication.

When penicillin and other measures fail to control the infections of the urinary tract streptomycin may be used. While streptomycin has not been used long enough to give final statements, it is helpful in the treatment of infections due to gram negative bacilli such as *Bacillus coli*. However its chief value seems to be in *Proteus amnioniae* and *Aerobacter aerogenes*. The dosage of streptomycin is 30 grams (2 gm) daily, divided into eight doses, for about one week. Streptomycin produces its best results if the urine is kept alkaline, but this is not resorted to until necessary because of the unfavorable toxic reactions which may occur. The toxic effects are similar to those of penicillin. However, streptomycin may be followed by nerve deafness, ataxia and dizziness, but these undesirable reactions usually clear up and are not permanent.

When the kidney infection is resistant to the medical measures given above, lavage of the renal pelvis by a urologist is recommended. (See note at end of section on Cystitis.)

FRANCIS D. MURPHY

CYSTITIS

Cystitis is a general term used to define any urinary tract infection in which there are bladder symptoms. Treatment of this condition is secondary and of far less import than to determine the primary cause of the bladder inflammation and to treat it adequately. This cause frequently lies in the upper urinary tract.

The treatment of cystitis itself may be classed into general and specific measures. The general measures include bed rest, fluid intake, heat applied to the suprapubic area, sedation, alkalization of the urine, and other symptomatic devices, specific measures consist of the use of chemotherapy, antibiotics, urinary antiseptics, arsenicals, and local measures directed to the bladder itself.

Since cystitis is really a term which signifies a symptom complex, the physician's first duty is to relieve the condition causing distress to the patient. In the acute stage of cystitis, bed rest is usually necessary and a liberal intake of fluids (enough to ensure an output of about 2 liters in 24 hours) is ordinarily quite important except in those cases where inflammation, extreme urgency, and frequency are present. Fluids in these cases might lead to polyuria and an aggravation of symptoms.

Heat applied to the suprapubic area or perineum, such as a hot-water bottle, hot rectal irrigation, or hot vaginal douches in the female, may also be of benefit. The judicious use of barbiturates and codeine, 30 mg., or in severe cases, morphine, 15 mg. may also bring symptomatic relief. An old time remedy which is apparently effective, although it is not too rational, is the use of opium and belladonna suppositories rectally.

Alkalization of the urine may be accomplished by the use of potassium citrate, sodium bicarbonate, citrocarbonate, or any alkaline mineral water. These alkalies, however, should be used only when they do not interfere with the chemotherapy given.

Frequency and urgency may be reduced by one of the bladder antispasmodics, particularly tincture of Hyoscyamus, 30 minims three times a day, or tincture of belladonna, 10 to 15 minims three times a day. In extreme frequency, the use of indwelling cath-

eter drainage for a short period may be necessary, or if tenesmus and stranguria are severe, the installation in the bladder of one of the topical anesthetics, such as novocain or procaine, 4 to 5 per cent, may be helpful from the purely symptomatic point of view. Free evacuation of the bowels is useful not only from the standpoint of making the patient more comfortable but also from that of reducing intestinal stasis which may be a factor in keeping the urinary tract infection alive or active.

Cystoscopy in the acute stage is definitely contraindicated and should be done only under special conditions as the bladder is too inflamed and easily irritated. The procedure is extremely painful in this condition and is another source of irritation that will cause the already existing pathology to flame up. Catheterization should also be avoided.

Before specific therapy is instituted in any urinary tract infection, one should obtain a culture of the urine to determine what the offending organism or organisms are. Following this, either chemotherapy or antibiotic therapy is indicated.

Of the sulfonamides, the most effective are sulfadiazine, sulfathiazole, or sulfamerazine. A full systemic dose of these drugs, however, is not necessary, as in urinary tract infections usually 30 grains (2 gm.), given in 0.5 gm. doses four times a day is sufficient to achieve high levels in the urine. Because of the small dose needed and because one always takes pains to assure a good urinary output, concomitant alkalization of the urine is not necessary and crystalluria is seldom seen.

Since the lower gastro intestinal tract is not an infrequent source of urinary tract infection, an attempt at sterilization of, or at least a reduction in, the bacterial flora, may be quite helpful. This may be accomplished with one of the poorly absorbed sulfonamides such as sulfasuxidine, 150 grains (12 gm.), daily or sulfathaladine, 60 to 90 grains (4 to 6 gm.), a day.

Penicillin, 20,000 or 30,000 units every 3 hours, or one of the slowly absorbed depository types of penicillin in a dosage of 200,000 to 300,000 units daily is helpful. This is effective in most gram positive infections of the urinary tract, however, the

great majority of urinary infections are caused by gram negative organisms which are resistant to penicillin

Streptomycin is an exceedingly effective urinary tract antiseptic, perhaps the most effective of all in that it is capable of eradicating certain types of gram negative infections which are resistant to all other types of therapy. The dosage is 25 to 30 grams (15 to 20 gm) daily. The untoward reactions of this form of therapy, however, must be borne in mind and its use should be properly reserved for those cases which prove resistant to the other usual types of treatment.

Mandelic acid and its derivatives are good urinary tract antiseptics in the treatment of gram negative infections and in the treatment of *Streptococcus faecalis* infections which are usually resistant to sulfonamide therapy. A urinary concentration approaching 1 per cent is necessary before these antiseptics may be used. This means that about 180 grains (12 gm) of the drug must be given in 24 hours to achieve a sufficiently high concentration. This is one of the few instances in which one purposely produces a diminished urinary output. The urine during mandelic acid therapy must be kept at a pH between 5 and 5.5 and urinary acidifiers must be given to achieve this desired degree of acidity. The use of mandelic acid should not be continued for more than 2 weeks as a clinical acidosis may result, nor should it be used in cases in which there is depressed renal function or in patients having gastro intestinal disturbances, as it is poorly tolerated. However, a mandelic acid derivative, mandelamine, has been shown to be about as effective, and in smaller dosages without producing gastro intestinal intolerance. Methenamine is one of the old urinary antiseptics and if used properly may be effective in doses of 75 to 150 grains (5 to 10 gm), in 24 hours associated with a urine acidifier, since this action depends upon the liberation of formaldehyde in the acid bladder urines.

There is a rare type of urinary tract infection, frequently severe and frequently diagnosed as cystitis, in which no organism can be demonstrated (the so called sterile pyuria or amicrobic pyuria). In these in-

flamations a viral etiology has been suggested. They are resistant to all the usual chemotherapeutic agents and antibiotics but respond dramatically to the arsenicals such as neoarsphenamine or mapharsen. The arsenicals are also helpful in certain types of staphylococcal infections which prove resistant to other types of therapy.

Local measures directed to the bladder are ordinarily not used during the acute stage but find their chief use in the treatment of chronic urinary tract infections. This form of treatment includes irrigation of the bladder cavity itself by use of the various types of irrigating solutions, such as potassium permanganate, 1:5000 saturated solutions of boric acid, normal saline, or acriflavine, 1:8000. These irrigations are carried out once or twice daily, about a liter of solution being used during the process. When alkaline incrustations are part of the bladder, their removal may usually be effected by dissolution with an acid irrigating solution such as phosphoric acid, 0.5 to 1 per cent acetic acid in the same concentration, or some of the buffer acid solutions such as Suby's solution (solution G or M). Silver nitrate solution in concentrations varying from 1:10,000 to 1:500, may be useful especially where bleeding is associated with the bladder inflammation.

The only type of true primary cystitis is that called interstitial cystitis, panmural cystitis, or Hunner's ulcer. This condition must be properly diagnosed by means of the typical history as well as the cystoscopic picture. It is a chronic form of cystitis of rather infrequent occurrence. Management is exceedingly difficult because of the chronicity of the condition and at times the extreme severity of the symptoms. Many types of therapy have been advocated. Careful bladder irrigations with or without benefit of anesthesia, and the use of increasing strengths of silver nitrate solution may be helpful at least temporarily. There is no specific therapy since the exact etiology is unknown.

Any acute cystitis which responds poorly or not at all to the usual measures after 2 weeks of therapy and all chronic cystitis must have a thorough investigation of the entire urinary tract, as a primary source will

unquestionably be found outside of the bladder*

FRANCIS D MURPHY

RENAL CALCULI

The management of both ureteral and renal calculi is usually the function of a trained urologist. However, the treatment of the acute attack often must be carried out by the general practitioner or internist, as surgery is not indicated in the treatment of all cases of ureteral or renal stone.

The size of the stone, its location, and the response to the infection by the use of drugs are factors which determine the mode of treatment to be carried out.

In the treatment of the acute attack, morphine, $\frac{1}{4}$ grain (0.15 gm), and atropine, $\frac{1}{100}$ grain (0.008 gm), must be given rapidly, if necessary every one half to one hour, until the pain is relieved. It is hardly worth while to temporize with other measures of palliation. It should be realized, however, that under conditions of anuria, chills and fever, persistent costovertebral angle pain and tenderness, or persistent intractable pain, some type of drainage must be instituted as an emergency measure.

In the period between the acute colicky attacks, measures must be used to clear up an associated infection and to bring about passage of the calculus. The preparations used for the infection are those enumerated above in the discussion of the treatment of pyelitis—the sulfonamides, penicillin, streptomycin, aureomycin, and chloromycetin.

As urinary stones may be of different chemical mixtures, it is necessary to determine if possible the kind of stone present in order to prescribe a routine of diet and treatment. They may include uric acid, calcium phosphate, cystine, or calcium oxalate stones. Special studies of the urine and the blood

are important in determining the nature of stones present. As an example, high blood calcium, that is, above 11 mg per cent, is suggestive of hyperparathyroidism which may have to be treated specifically by removing tumors of the parathyroid glands. The urinary pH most favorable for the dissolution of the kind of stone present is indicated. One must provide for a fluid intake of from 4000 to 6000 cc a day as well as to employ the antibacterial agents necessary for the control of the infection. If a small renal stone is passed, the nature of this stone should determine the subsequent routine to be prescribed for a patient in an effort to prevent the formation of other stones. Large stones which obviously will not pass must be treated surgically.

Where no specimen of stone is obtainable to determine its nature, the urinary pH and the consideration of infection as well as the kind of crystals in the urine may be helpful. When the nature of the stone is known, such as carbonate or phosphate stones, the following formula has been recommended for dissolving the calculi. This formula is known as solution G and is as follows:

Citric acid (monohydrate)	32.25 gm
Magnesium oxide (anhydrous)	3.84 gm
Sodium carbonate (anhydrous)	4.37
Water ad	1000 cc

The formula is administered by means of ureteral catheterization.

FRANCIS D MURPHY

REFERENCES

* Aureomycin and chloromycetin are now known to be valuable agents in the treatment of urinary tract infections. These drugs are of value against most of the usual bacterial invaders of the urinary tract except *B. proteus* and *B. pyocyaneus*. The usual method of administration is 500 to 750 mg every 6 hours. Polymyxin, a new antibiotic, is effective against organisms of the *Pseudomonas* group which are not vulnerable to aureomycin or chloromycetin. The specific dosage of polymyxin cannot be stated at the time of this writing.—Editor

- Addis T. *Glomerular Nephritis, Diagnosis and Treatment*. New York: The Macmillan Company, 1948.
- Addis T. Osmotic Work of Kidney and Treatment of Glomerular Nephritis. *Tr A Am Physicians*, 55:223, 1940.
- Bell E. T. Lipoid Nephrosis. *Am J Path*, 5:387, 1929.
- Blackfan K. D. and Mills C. A. The Effect of Two Per Cent Magnesium Sulphate Solution on the Cerebral Symptoms of Acute Nephritis. *Tr Am Pediat Soc*, 35:197, 1923.
- Chanutin A. and Ferris E. B., Jr. Experimental Renal Insufficiency Produced by Partial Nephrectomy. *Control D et Arch Int Med*, 49:767, 1932.
- Christian, H. A. *Bright's Disease in Oxford Medicine*. New York: Oxford University Press, 1948, Vol 3 p 583.
- Epstein, A. A. Concerning the Causation of Edema in Chronic Parenchymatous Nephritis, for Its Alleviation. *Am J Med Sc*, 154

- Farr L E and Smadel J E Influence of Diet on Course of Nephrotoxic Nephritis in Rats *Proc Soc Exper Biol & Med* 36:472 1937
- Farrar G E Jr Sackett C F and Long J H Management of Nephrotic Syndrome *Am Pract* 2:194 1947
- Harvey A McG et al Therapeutic Conference The Treatment of Heart Failure *Bull Johns Hopkins Hosp* 81:430 1947
- Kempner W Treatment of Hypertensive Vascular Disease with Rice Diet *Am J Med* 4:545 1948
- Kremen A J Problem of Parenteral Nitrogen Administration in Surgical Patients with Special Consideration of Preoperative Preparation and of Means of Effecting Favorable Nitrogen Balance *Surgery* 23:681 1948
- Murphy F D Relation of Diet to Various Forms of Bright's Disease *J Am Diet A* 15:13 1939
- Murphy F D and Peters B J Treatment of Acute Nephritis Immediate Results and Outcome 10 Years Later in 89 Cases *JAMA* 118:183 1942
- Murphy F D and Pietraszewski B J Effect of Acid Ash and Alkaline Ash Diets in Treatment of Acute Glomerulonephritis *Internat Clin J* 12:1940
- Murphy F D and Wood W D Acute Nephritis and Effect of Sulfonamides on Kidneys *Ann Int Med* 18:999 1943
- Rubin M I and Rapoport M Mode of Action of Magnesium Sulfate in Reducing Hypertension of Acute Glomerulonephritis *Am J M Sc* 201:734 1941
- Salvesen H A The Effect of Blood Transfusions on the Kidney Function of Chronic Nephritis with Anemia *Acta med Scand nav* 131:337 1948
- Seligman A M Frank H A and Fine J Treatment of Experimental Uremia by Means of Peritoneal Irrigation *J Clin Investigation* 25:211 1946
- Smalley H E et al Effect of Intravenously Administered Solution of Acacia on Animals *Arch Int Med* 76:111 1945
- Spence H Y and Sutton L E Jr The Nutritional Management of the Nephrotic Syndrome *Virginia M Monthly* 75:418 1948
- Strauss M B Acute Renal Insufficiency Due to Lower Nephron Nephrosis *New England J Med* 239:693 1948
- Thorn G W and Tyler F H Clinical Management of Edema in Bright's Disease *M Clin North America* 31:1077 1947
- Volhard F in *The delph a*
- Volhard F *Der Arterelle Hochdruck und die der deutsch Gesell f inn Med* 35:184 1923

DISEASES OF THE LOCOMOTOR SYSTEM

RHEUMATOID ARTHRITIS

Diagnosis. Rheumatoid arthritis is a chronic, generally progressive disease, manifested primarily as a destructive and deforming articular inflammation. Characteristic complications include subcutaneous nodules, nodular inflammation of muscles and nerves, ophthalmitis, anemia, vasomotor disturbances, muscular atrophy, loss of weight, hypertrophy of lymph nodes and, in some cases, a chronic progressive inflammatory carditis. The disease occurs at all ages in children, in mature adults, and in the aged. In most cases, however, it first appears between the ages of 20 and 40.

The cause is unknown. Search for the re-

ected to the possibility of a hormonal etiology by discovering the efficacy of the adrenal cortical hormone, cortisone, 17-hy-

however, has not disclosed the etiology of rheumatoid arthritis, and the manner in which these substances, or some modification of them, will eventually be used for treatment remains to be established. There is now reason to believe, however, that rheumatoid arthritis will become susceptible of effective control.

Two major types of rheumatoid arthritis are encountered, but these are not always distinct and some individuals display a mixture of the two, with the clinical features of one or the other predominating. In the first type, joints of the extremities are chiefly affected. This variety may be designated the peripheral type. A second variety affects the spine primarily and is variously designated as rheumatoid spondylitis, Marie-

Strumpell disease, von Bechterew's disease, adolescent spondylitis, spondylitis deformans, etc. The peripheral type predominates among females, its incidence being two to three times greater than in males. The spinal variety, on the other hand, is most commonly encountered among males, its incidence being 10 to 20 times as great as among females.

The usual mode of onset for both types is insidious although it may be precipitous. Ordinarily, patients observe stiffness and swelling in several joints, complain of fatigue, loss of weight, and pain on motion. Joints which are affected become visibly swollen, tender, and sometimes discolored. Only a few scattered joints may be involved, but in the more typical cases multiple joints are attacked in a symmetrical pattern. In its advanced stages, rheumatoid arthritis cannot readily be mistaken for any other disease, the patient presenting a picture of which the predominant features are symmetrical articular swellings, capsular contractures, flexion deformities, inanition, subcutaneous nodules, wasting of muscles, and various trophic skin disorders.

Laboratory data may aid in establishing a diagnosis and may provide assistance in

is usually elevated and the globulin fraction of serum proteins is commonly increased relative to the albumin fraction, the albumin-globulin ratio being often reduced or actually "inverted" in consequence. Leukocyte counts generally are within normal limits although occasional variations are encountered. Acute cases may show a leukocytosis of between 10,000 and 20,000. Rarely, in cases of long duration, the total leukocyte counts are low, ranging between 2000 and 4000 per cubic millimeter.

In the earlier stages of rheumatoid ar-

thrits roentgenograms generally disclose swelling of soft tissues about joints and atrophy of subarticular epiphyseal bone. In more advanced cases roentgenograms show narrowing of articular spaces and erosion and atrophy of articular cartilages. In late stages erosions and destruction of epiphyseal bone may be seen.

Treatment **GENERAL COMMENTS** Physicians approaching the problem of treatment for rheumatoid arthritis must take many factors into account. It is essential first of all to realize that no single remedy which is regularly effective is available at this time. Consequently treatment should be planned for each patient in the form of a program made up of many parts each directed toward a separate aspect of the disease. The patient's economic status must be taken into consideration. Ideal care might perhaps entail prolonged hospitalization with professional physical therapy, supervision of diet and frequent laboratory controls. Such ideal treatment is rarely available for a patient with rheumatoid arthritis and in consequence a physician must be willing to make an appropriate compromise. Home measures of physical therapy often must be substituted for more elaborate professional treatments. Home made splints and supports may have to serve in lieu of custom made ap-

pliances which can be carried out largely by the patient with the aid of members of his family.

Physicians should keep in mind also that the therapeutic program must be altered from time to time as the manifestations of the disease alter in a never ending variety. At one period a patient may be completely helpless requiring constant nursing care. During this period he may have intense pain and may require narcotics. At another period he may have little in the way of constitutional disturbances and his articular disease may cause only minor inconvenience. A program of treatment suited to the first situation will obviously not be appropriate for the second.

An important aspect of treatment in this condition is the matter of informing the patient regarding the nature of his illness and

the procedures which he should employ in its treatment. Thoughtful discussions between patient and physician are of great value for this purpose. These discussions should provide the physician with opportunity to stress the need for patience and perseverance with treatment measures and to stress the value of such perseverance in improving the outlook both as to eventual recovery and to the avoidance of deformities.

In general the treatment of rheumatoid arthritis will be discussed on the following principles: (1) rest and regulation of activities (2) physical therapy (3) occupational therapy and psychotherapy (4) rehabilitation (5) roentgen therapy (6) fever therapy (7) heliotherapy (8) vitamin therapy (9) foci of infection (10) chrysotherapy (11) general measures and (12) cortisone and ACTH. Perhaps developments of the near future will alter this list notably but the time has not yet arrived when these measures can be effectively supplanted.

REST Of these several procedures rest is perhaps the most important although its significance may be modified as increased experience is gained with pituitary and adrenal hormone therapy. Until that experience has been accumulated however rest should not be neglected its value although empiric is well established.

Prescription for rest should be given in detail. Each patient presents an individual problem. Some terribly debilitated and suffering with active articular inflammation require almost continuous rest in bed. To prescribe complete rest for all patients however is unrealistic and unless such advice is accompanied by directions for regularly continued physical therapy the advice may prove harmful. Patients in whom the disease is inactive may be permitted nearly a normal degree of activity. Between these two extremes lies a program of rest applicable to cases of intermediate severity. For the "average case" 10 hours of rest in bed at night and 2 or 3 hours of additional rest during the day generally will suffice. In addition certain joints more acutely affected than others or threatened with contractures may require local aids to rest such as splints, partial casts or other supports.

In short rest should be employed for rheu-

matoid arthritis just as one would employ this measure in treatment of other chronic diseases. The design should be to encourage the natural healing processes. Overemphasized rest may result in excessive muscular weakness favor the development of deformities from disuse and unnecessary undermining of the economic status of wage earners. On the other hand underemphasis on rest may produce results which are equally undesirable. For example some patients instructed to exercise lest the joints "lock" drive themselves in an attempt to maintain activity thus aggravating the exhaustion which usually accompanies the disease. Others wiggle their joints constantly thus aggravating local inflammatory processes. A proper degree of emphasis to place upon both rest and activity should be determined by the physician after consideration of the condition of each individual patient.

PHYSICAL THERAPY Physical measures of value for most patients include applications of heat, massage and exercise. Details concerning the use of these procedures belong in textbooks on physical therapy rather than here, but a few points are mentioned for general guidance.

Heat. Apparatus for applying heat must be adapted to each individual's situation. Where electricity is not available patients can resort to warm tub baths, hot compresses or the use of warmed bags of grain or salt. Hot water bottles, electric pads, infra red bulbs or home made bakers are available to the average city dwelling patient.

Infra red lamps are commonly used by patients to whom electric current is available. They should be conveniently mounted on a stand and employed with a reflector similar to the type used in connection with photographic illumination. Two hundred and fifty watt "mazda" CY bulbs or 200 watt carbon filament bulbs are economical and convenient.

For heating larger areas with infra red radiation an inverted cradle like apparatus within which are supported incandescent bulbs is effective. Such electric bakers are especially useful where the spine or lower extremities require treatment. Directions for making a satisfactory baker may be obtained

from the Council on Physical Therapy of the American Medical Association.

Warm paraffin can be conveniently employed for heating joints. Four to 6 lbs. of paraffin are placed in the top compartment of a double boiler and warmed to melting by heating water in the lower compartment. In this manner the wax is protected against catching fire. When melted the wax may be allowed to cool until a thin film forms on the surface. Hands may then be dipped slowly in and out of the wax 10 or 12 times. The glove of wax thus formed is then allowed to remain on the hands about 20 minutes after which it may be peeled off and returned to the pan for further use. Warm liquefied wax may be painted on other joints with a paint brush.

Massage. The purposes of massage are maintenance of muscle tone, prevention of muscle atrophy and alleviation of spasms and contractures. In rheumatoid arthritis muscles about affected joints may be massaged daily. A family member can be taught to give massage at home thus dispensing at least partially with the need for expensive professional massages. However, home physical therapy should be supplemented by professional treatments once or twice weekly if possible.

Exercises. Most physical therapists recommend a period of exercises following heating and massage. These exercises should be appropriate to the situation presented by each individual patient. In the case of joints which are extremely painful, exercises must be performed gently, perhaps with the assistance of a technician or trained member of the family. If the joints are less painful, exercises may be more active or may even be performed against resistance.

Experience indicates that deformities and contractures may be minimized by a carefully planned program of physical therapy which includes exercises during which affected joints are moved through their full

range. Physicians who plan occupational therapy for arthritic patients. Occupational activity should consist of work which is interesting, the work chosen should entail articular and muscular movements calculated to maintain

and improve action of affected joints it should not be excessively tiring Occupational therapy which has been properly planned may serve as an important aid in ridding patients of feelings of helplessness and dependency

PSYCHOTHERAPY There is a place for psychotherapy in the treatment program of patients with rheumatoid arthritis but the value of this measure should not be exaggerated Patients with rheumatoid arthritis may suffer exacerbations coincident with or subsequent to unusual psychologic stresses Hence these should be avoided if possible One valuable and effective measure of psychotherapy for patients with rheumatoid arthritis is a well ordered therapeutic program prescribed by a physician whose manner indicates reasonable optimism and confidence

OCCUPATIONAL AND PHYSICAL REHABILITATION In the past little attention has been paid to this aspect of the treatment of patients with rheumatoid arthritis but there is a need for rehabilitation procedures in many instances A strong effort should be made to maintain or establish economic usefulness for each patient Occupations should be chosen to fit physical capacities Ideal employment should maintain earning capacity without requiring excessive physical exertion Patients with rheumatoid arthritis usually cooperate willingly in making such plans and often display a remarkable degree of hardihood, tolerating much pain and fatigue in order to stay on the job This praiseworthy tendency needs to be encouraged as much as possible but patients should not be encouraged to work at occupations which aggravate the disease by traumatizing inflamed joints

During World War II rehabilitation procedures were organized systematically for arthritic patients at the Army Rheumatism Center in Hot Springs Arkansas Included in that program were such activities as gardening calisthenics pursuance of constructive hobbies and classroom instruction in various subjects These procedures often aided effectively in re-establishing employability of demoralized patients who had spent many months in military hospitals and it is reasonable to believe that activities such as were employed at the Army and

Navy hospital can be adapted to nonmilitary medical centers

ROENTGEN THERAPY Treatment of rheumatoid arthritis of peripheral joints by x rays has been generally discarded because controlled studies have failed to demonstrate any significant improvement following its use On the other hand roentgen therapy is being widely used for rheumatoid spondylitis Recommended technics for treatment of spondylitis are given in later paragraphs

FEVER THERAPY The popularity of fever therapy for rheumatoid arthritis reached a peak in America during the middle 1930's but this measure now has few proponents

recommend brief periods of cabinet therapy in order to prepare patients for massage and exercises For this purpose the duration need not exceed 30 to 40 minutes and body temperature need not be elevated beyond 99 or 100° F

Fever therapy by means of intravenous typhoid vaccine therapy continues in use by many rheumatologists This procedure may occasionally be followed by notable subjective improvement The author continues to use typhoid vaccine therapy for patients with active rheumatoid arthritis when an excessive degree of debility or anemia is not present and when arteriosclerosis is not advanced

given at intervals of two or three times a week Courses may be repeated at intervals of 6 months to a year if the first trial results in some improvement The first injection of each course should consist of 10 000 000 or 20 000 000 organisms Thereafter the dose may be doubled for each subsequent injection The patient's temperature should be checked hourly during the postinjection period until fever has subsided Thirty milligrams of codeine may be given for severe headache or for unusual muscular or articular pain Fluids should be given freely during the period of fever and a nurse or members of the family should be prepared to sponge the skin if an undue elevation of temperature occurs Typhoid vaccine fever

therapy is safe if carried out in this fashion

HELIO THERAPY No evidence has been produced to indicate that sun bathing can favorably influence the course of rheumatoid arthritis. However sun bathing is well tolerated and there is little to be said against it. Sun baths should not be used to the exclusion of other more rational forms of treatment.

VITAMINS During the past two decades the potential value of vitamins as a treatment measure for rheumatoid arthritis was carefully explored. In general this work resulted in negative conclusions. At present most experienced rheumatologists have concluded that no definite therapeutic value has been proved for any vitamin which has been applied in the treatment of rheumatoid arthritis.

THE MANAGEMENT OF FOCI OF INFECTION Although the theory that rheumatoid arthritis is caused by focal infection is being generally abandoned, experienced rheumatologists still search for infected foci while examining patients with the disease. This is generally done in the belief that infectious foci may lower healing powers or resistance. Radical treatment of suspicious foci rarely results in spectacular improvement of rheumatoid arthritis; therefore surgery for a suspected focus should be undertaken only if the operation can be accomplished without notable risk.

Teeth In dealing with dental problems in patients with rheumatoid arthritis it is important to preserve adequate masticating surfaces so far as possible. Useful teeth should therefore never be sacrificed on the basis of a mere suspicion. Devitalized teeth are not always infected and should not be removed as a treatment measure for the arthritis. Deep pockets of pyorrhea should receive local treatments aimed at preserving the life of adjoining teeth. Teeth having definite periapical abscesses should be removed and fragments of dental roots which may have been left following previous faulty extractions should also be removed.

Tonsils Tonsillectomy is a justifiable procedure in a patient with rheumatoid arthritis if the tonsils are grossly infected or if they have been the sites of repeated acute infections. In a majority of the cases this problem does not arise today because the tonsils have

usually been removed prior to onset of the arthritis.

Sinuses Indications for the treatment of infected sinuses in arthritic patients are identical with those which obtain in nonarthritic patients. Suppurating sinuses should be provided with adequate means of drainage but operations on sinuses should not be undertaken merely on the basis of "suspicious" or "cloudy" appearances of sinuses in roentgenograms.

Other Foci The cervix should be examined for evidences of infection in every female with rheumatoid arthritis. Local treatment should be instituted only if clear cut evidence of infection is encountered.

Prostatic secretions obtained following massage should be examined in male patients who have an otherwise unexplained pyuria. Secretions which show more than 15 or 20 pus cells in each high power microscopic field may indicate the presence of infection. In such instances local treatment with massage may be given once or twice weekly together with occasional brief courses of penicillin or sulfonamides.

Diseases of the *gallbladder, appendix, colon, etc.* are no more frequent in patients with rheumatoid arthritis than in nonarthritic patients. When infection is detected treatment should be planned according to rules which apply in patients without rheumatoid arthritis.

CHRYSOTHERAPY Treatment of rheumatoid arthritis with gold was introduced by European physicians in 1927 but in America little attention was given to this subject until nearly a decade later. Since then gold has been used to an increasing extent by physicians in this country and during the past 5 years has largely supplanted the use of other injectable substances. Although some careful students of rheumatic disease still insist that the beneficial value of gold has not been established, those who hold this view are in the minority. The practicability of its use has been increased by the discovery that BAL is an effective treatment for some of the toxic manifestations which may appear during chrysotherapy.

Dissemination of information to laymen regarding toxicity of gold has been a source of difficulty in making use of this. This publicity has caused

sion among some patients and it is not uncommon now to encounter individuals seriously afflicted with rheumatoid arthritis who cannot be persuaded to submit to gold therapy because comments in the lay press have made them fearful of toxic reactions.

Publicity which has been given to discovery of the antiarthritic effects of cortisone and the pituitary adrenocorticotrophic

available are reluctant to begin a tedious course of injections with gold. Until such time as these hormones become available in

quantity and until their usefulness and limitations are more fully understood chrysotherapy will continue to occupy an important place in the vigorous treatment of rheumatoid arthritis. On that account its use will be discussed at some length.

Choice of a Preparation. The compounds of gold most frequently used in America are listed in Table I. Colloidal suspensions once popular have largely been discarded in favor of more readily absorbable preparations soluble either in water or in oil. No one preparation is demonstrably superior to any of the others which are commercially available at this time.

Chemical Name	Proprietary Name	Solubility in Water	Physical State	Gold Content (Per cent)
Gold sodium thiosulfate	Sanochrysine	+	Aqueous solution	37
Gold sodium thiomalate	Myochrysine	+	Aqueous solution	50
Gold thio glucose	Solganal B oleosum	—	Oil suspension	50
Gold thioglycol anilide	Lauron	—	Oil suspension	54

Dosage and Methods of Administration. All preparations should be given intramuscularly. There is no justification for intravenous administration. A regimen which is commonly used in the case of myochrysine and sanochrysine is as follows: Beginning with 10 mg. doses are increased progressively to 25 mg. Injections should be given twice weekly rather than once and should be continued until the patient has received

following completion of the initial course.

Relapses. Follow up studies of gold therapy have shown a high incidence of relapses (up to 75 per cent of the cases). Approximately 50 per cent of such relapses occur within the first year following treatment. This high incidence may be less under the continued treatment described above than under the discontinuous treatments which were formerly employed. Relapses do not always respond to further treatment with gold.

Mode of Action. The mechanism by which

gold produces its supposed benefits in rheumatoid arthritis is unknown. Gold salts possess bacteriostatic and chemotherapeutic properties against a number of microorganisms but the benefits resulting from gold therapy in rheumatoid arthritis can scarcely be related to these properties since the disease is not believed to be of bacterial origin. An effect on some enzyme system has been considered but there is no proof of such an effect and no information to relate it to the relief of rheumatoid arthritis.

Metabolism of Gold Salts. Soluble compounds of gold are absorbed slowly from the site of their deposit in the muscles. Small amounts appear in the plasma within a few hours after an injection and later may be found in almost every cell of the body. The greatest concentrations appear in the liver, spleen, kidneys and skin. Approximately 75 to 90 per cent of the amount which is excreted appears in the urine and the balance appears in the stools. The excretion rate is slow and is continued for a long time; some gold has been demonstrated in urine 13 months after administration of the drug and

in plasma 10 months following its administration

Results of Gold Therapy in Rheumatoid Arthritis Satisfactory and even impressive results have been claimed for gold therapy by many writers on the subject, although some others have found no evidence of its benefits. In a recently published review on gold therapy, Sundelin noted improvement rates varying from 40 to 95 per cent among reports of 3 800 patients treated. The median improvement rate was 81 per cent. Regarding these reports, some critics of gold therapy have objected that such claims were unjustified because comparison was not always made with improvement rates in untreated cases. This criticism cannot be wholly answered today because studies conducted thus far have not been sufficiently objective to satisfy rigid experimental requirements.

Toxic Reactions to Gold Toxic reactions are not infrequent during gold therapy and must be given serious consideration by a physician who employs this treatment. The risks of toxic reactions should be discussed with the patient, and where possible with other family members, so that all will understand and share with the doctor the responsibility for any untoward occurrence. The incidence of all toxic reactions has been reported as varying from 21 to 88 per cent. However, serious toxic reactions occurred in only 4 or 5 per cent of the author's series of patients who have been treated according to the plan outlined above. Prior to 1942, fatalities reportedly occurred in approximately 1 in 200 to 1 in 300 patients. This incidence may be lower now because of the effective use of BAL in treating serious toxic reactions to gold.

The toxic manifestations most frequently encountered affect the skin and mucous membranes. These may range from mild pruritus or minor stomatitis to an intense exfoliative dermatitis. Hepatic and renal lesions, reactions affecting the nervous system (peripheral neuritis, encephalitis), and

lytic anemias have been most prominent.

Little is known concerning the pathogenesis of these toxic reactions although it seems certain that these reactions reflect

something other than simple intoxication with the gold metal. Serious and even fatal reactions have followed administration of a few doses containing an amount of gold too small itself to provoke a toxic reaction.

There is no sign on which we can rely as an indication of the approach of toxicity. A drop in the platelet count to less than 75,000 per cubic millimeter of blood, a lowering of leukocyte counts to less than 4,000 per cubic millimeter, a rise of eosinophil counts, the appearance of albumin or erythrocytes in the urine—all of these may be danger signs and should be regarded as warnings. In some instances, pruritus has preceded serious skin reactions. The physician should stop gold therapy immediately on the appearance of any of these warning signals, but he should also bear in mind that important toxic manifestations may appear without any prelim-

should be given to use of BAL. Mild symptoms which at first may be regarded as evidences of gold reactions sometimes disappear without special treatments.

BAL (British anti lewisite, 2, 3, -dimer-captopropanol) which was developed in Great Britain during World War II as an antidote for arsenical gas burns, has proved its value in the treatment of poisoning by gold and other heavy metals. Recent investigations have disclosed that gold, as well as

protein from these combinations, forming tight metal-BAL compounds which are inert. The metal, thus rendered nontoxic, is excreted by the body at leisure.

Examples of gold toxicity which have responded satisfactorily to BAL therapy include exfoliative dermatitis, thrombocytopenic purpura, granulopenia, stomatitis, conjunctivitis, and nephrosis.

BAL is dispensed in a 10 per cent solution in peanut oil containing 20 per cent of benzyl benzoate. It is administered intramuscularly, first in intervals of 4 to 6 hours for 1 or 2 days, subsequently twice daily for 2 or 8 days, then once daily until the last

evidences of toxic reaction have disappeared. The dose is 25 mg (0.025 cc of the solution) for each kilogram of body weight. In most instances toxic reactions have subsided within a week or 10 days under this treatment. In some cases treatment has had to be continued for 2 or 3 weeks.

This substance has itself been responsible for a notable incidence of toxic reactions. These have included malaise, nausea, vomiting, salivation, lacrimation, sensations of warmth and abdominal pain. Injections are sometimes painful and local abscesses have been observed.

In general a relatively great risk from gold intoxication justifies the slighter risk of toxicity from BAL. However, a small dose of

reactions, some of which clear spontaneously following discontinuation of gold therapy, one may properly observe the patient closely for a few days and in this manner attempt to avoid the need for BAL. If indications point to a progressive toxicity, however, BAL should be given without delay.

Complete blood counts once monthly are adequate for most patients. Additional laboratory controls should be employed whenever a suspicion is aroused that some toxic effects may be developing.

Tentative Conclusions Regarding Gold Therapy. The position which gold therapy may eventually occupy in the field of rheumatism is uncertain. The risks which accompany it, though less by virtue of the discovery of BAL, are still notable and therefore prudence dictates that gold should be used only by those who have facilities for repeated laboratory studies of blood and urine. Occasional patients show striking improvement during treatment, but the quality of this improvement cannot be compared in most instances to that which is encountered in patients who have acquired intercurrent jaundice or in women patients who have become pregnant. Neither does the effect of gold compare with the immediate effects produced by cortisone and the pituitary adrenocorticotrophic hormone. However, un-

til the latter substances become more plentiful and until their long term use has been further explored, the continued use of gold is justifiable. Gold should not be used as a therapy for any articular disease such as rheumatoid arthritis and possibly psoriatic arthritis. There is no justification for its use in osteoarthritis or in fibrositis.

OTHER MEASURES. *Dietotherapy.* Prescriptions for special antiarthritis diets have been singularly absent from the medical scene in recent years. In most instances a well balanced diet adequate in vitamins and containing sufficient bulk to combat constipation is all that is necessary. In the case of patients who have lost considerable weight, various means may be attempted to increase the caloric intake. The addition of small

Patients who are overweight should be encouraged to lose weight.

Analgesics and Sedatives. An important part of the treatment program for a patient with rheumatoid arthritis is a proper prescription of analgesics. Salicylates are ineffective in relieving the fundamental process but nevertheless are usually effective temporarily for relieving stiffness and soreness. Most patients can secure comfort by taking 10 or 15 grains (0.6 to 1 gm) of aspirin in the morning on arising and at intervals during the day. Untoward reactions to salicylates used in this manner are extremely rare. Some patients tolerate enteric coated salicylate tablets better than uncoated tablets.

Small doses of barbiturates, for example, phenobarbital in doses of $\frac{1}{2}$ grain (30 mg) to $1\frac{1}{2}$ grains (90 mg) are useful in allaying restlessness and aiding sleep.

Narcotics are needed occasionally when pain is severe as during an acute exacerbation or following some unusual traumatic episode. For such instances codeine 30 mg or demerol 100 mg may properly be used. It is vitally important for the physician to keep in mind, however, that rheumatoid arthritis is essentially a chronic disease and that administration of narcotics is always attended by a possibility of addiction. It is better for the patient to submit himself to discomfort from articular pain than to run this risk of narcotic addiction.

Orthopedic Measures. This paragraph might properly be an extensive one including a review of operative and nonoperative measures which are of use in overcoming deformities and in maintaining mobility of affected joints. The nature of this section, however, does not permit detailed treatment of this subject and therefore only a few principles will be mentioned. Joints should be maintained in optimal positions by exercises, careful manipulations, by use of pillows, plaster supports, light weight splints, and simple traction apparatus when indicated. In chronic stages of the disease, the experienced orthopedist may provide valuable aid by arthroplasties, arthrodeses, synovectomies, and occasionally by osteotomies. In many instances, the patient's interests are best served when his treatment is directed both by an internist and an orthopedic surgeon.

CORTISONE (COMPOUND E) AND PITUITARY ADRENOCORTICOTROPIC HORMONE IN RHEUMATOID

treatment of rheumatoid arthritis is in progress. Much of this work is still incomplete and many questions regarding proper use of both compounds, and especially regarding long term effects, are still unanswered. However, both products are now available for use by physicians in many parts of the country.

treatments

Administration of both cortisone and of pituitary corticotropin results in almost every instance in a lessening of symptoms and in an improvement of articular swelling and tenderness. Systemic manifestations tend to abate under the influence of these hormones. In a majority of the cases, these benefits are apparent only during periods when administration is continued and regression usually occurs within a few hours or days after treatments are discontinued. It has become apparent, therefore, at least in relation to rheumatoid arthritis, that cortisone or corticotropin treatments must be continued for

longed use of these products is not sufficient to provide complete reassurance as to the safety of these long term measures. It has been determined, however, that in most cases patients tolerate these hormones reasonably well for periods of 4 to 12 months.

The degree to which an individual patient may show improvement with cortisone or with corticotropin depends in part on the duration of his illness before beginning treatment. Also important for determining the outcome is the factor of intensity of the articular and systemic manifestations. Patients in whom symptoms have been present for periods up to 6 months or even for as much as a year, may show remarkable improvement immediately following the beginning of cortisone or corticotropin treatment. In such instances, pain and swelling may be almost entirely relieved and a sense of well being may be greatly augmented. In more advanced cases results of treatment are determined largely by the severity of articular destruction present at the beginning of therapy. In cases where joints have been extensively damaged, functional improvement may be slight or even insignificant, deformities of advanced degree are not overcome, subluxations are not altered, and ankyloses are not relieved. In the most severe and advanced phases of the disease, in the so-called arthritic "derelict," recognizable benefits from the use of cortisone may be confined to an improved sense of well being,

the following plan for dosage schedules has been followed in preliminary experiments. Maximal daily doses of 100 mg. have been found sufficient for adults with rheumatoid arthritis. This amount should not, in general, be exceeded. In treating children, the amount of cortisone needed to control symptoms of

effective in providing reasonably satisfactory control of symptoms.

As regards cortisone, satisfactory effects have been achieved by means of single daily doses. The product available at present should be administered intramuscularly although it is anticipated that oral administra-

tion of cortisone will be feasible in the future

In order to provide a period for metabolic recuperation injections of cortisone may be given on 6 days of each week and injections may be omitted for several (3 to 7) consecutive days once monthly. Results obtained by administering cortisone on alternate days and by administering alternating larger and smaller doses have not yet been thoroughly explored but appear to be inferior to results with more uniform daily treatment.

(2) *Pituitary Corticotropin*. Duration of the action of pituitary corticotropin available today is brief generally in the neighborhood of 6 to 8 hours. Hence it is advisable in using this product to divide the daily dose into three or four portions and to administer these at intervals of 6 or 8 hours. Potency of the products presently available is not always uniform but most patients respond satisfactorily to amounts ranging between 60 and 80 mg daily. For children amounts required are proportionately smaller. A satisfactory rule to determine dosage for children is to start with a daily amount equivalent to 1 mg per kilogram of body weight increasing or decreasing this amount as indicated by the response of the individual.

Pituitary corticotropin available at present should be administered intramuscularly.

Hyperadrenalism (Cushings Syndrome) from Cortisone and Corticotropin Treatment of Rheumatoid Arthritis. Prolonged administration of either cortisone or corticotropin in large amounts may induce in some sensitive individuals symptoms of hyperfunctioning of the adrenal cortex. The resulting illness is similar to that which is seen with the spontaneously occurring Cushing's syndrome. Earliest evidence of this effect is rounding of the face with production of an appearance which has been designated moon face. A degree of edema of the lower extremities has been observed together with an acneiform eruption on the face, neck and back, subcutaneous ecchymoses, feeling of fatigue and even mental depression. These symptoms should be searched for constantly during treatment with cortisone or corticotropin and their appearance should indicate a need for at least temporary cessation of treatment.

Arterial hypertension has not appeared in

patients previously normotensive and patients with moderate degrees of arterial hypertension have been able to tolerate treat-

ment as this condition is invariably aggravated by cortisone or corticotropin treatment. It is not yet known whether diabetes mellitus should be considered a complete contraindication to use of these hormones, however, as it may be possible by employment of insulin and proper diet measures to avoid serious difficulties in such cases while at the same time providing relief from symptoms of rheumatoid arthritis.

Rarely intense nervous excitement has been observed following the use of both compounds and in some instances this symptom has progressed to a condition of outspoken psychotic behavior. It is urgently recommended therefore that every patient who is receiving cortisone or corticotropin treatment be observed closely for signs of such abnormal behavior. Treatments should be discontinued immediately when there is a suspicion that unusual nervous tension is being produced.

Cortisone and Pituitary Corticotropin in Treatment of Juvenile Rheumatoid Arthritis (Still's Disease). Patients with juvenile rheumatoid arthritis respond to treatment with these compounds similarly to adults. Signs of hyperadrenalism have been observed in children receiving this type of treatment and precautions regarding dosage schedules should be employed as outlined for the treatment of adults.

Rheumatoid Spondylitis. Results with rheumatoid spondylitis have been comparable to those seen in rheumatoid arthritis of peripheral joints. Dosage schedules required are similar to those for rheumatoid arthritis of peripheral joints.

Rheumatoid Arthritis with Psoriasis and Psoriatic Arthritis. Patients with these conditions have responded similarly to patients with rheumatoid arthritis if the classic form not accompanied by psoriasis. Partial or complete clearing of both arthritis and psoriasis has generally been observed in such cases.

Rheumatoid Spondylitis. The general principles which govern treatment of rheumatoid arthritis affecting peripheral joints

are applicable also to treatment of rheumatoid spondylitis. Some special procedures for this disease require additional comment.

Measures for the prevention and correction of the special deformities which occur in rheumatoid spondylitis should be advised in every case. Among the instructions to such patients postural and deep breathing exercises should be stressed. Where deformity has developed and the patient is stooped, efforts should be directed toward regaining lost height by stretching exercises and physical therapy procedures.

ROENTGEN THERAPY Although roentgen treatment for rheumatoid arthritis of peripheral joints has been abandoned by almost unanimous consent, there is still some enthusiasm for this treatment in connection with rheumatoid arthritis of the spine. Some patients report a lessening of pain, tenderness, and subjective stiffness, and show an increase in chest expansion after x-ray treatments. At least, this treatment does no harm when carefully administered. There is a risk of inducing sterility in young women by such therapy and this possibility must be given careful consideration in every instance when treatment is being planned for a female patient. If a woman may eventually desire to have children, it is best to avoid this therapy.

A technic for roentgen therapy of rheumatoid spondylitis widely used today is as follows: 200 kilovolts with 0.5 mm of copper and 1 mm of aluminum filtration, a half-value layer of 0.9 mm of copper and a 50 cm skin target distance with an output of 50 m measured in air per field (usual size of field 200 to 300 sq cm). Each portion of the spine treated can be given 600 roentgen units. Following completion of a treatment course, the process can be repeated once or twice if recrudescences occur and if the initial treatment has been productive of any promising results.

CHRYSOTHERAPY Most American rheumatologists have abandoned gold therapy as useless in the case of spondylitis.

EDWARD F. ROSENBERG

REFERENCE

- Hench, P. E., et al. The Effect of a Hormone of the Adrenal Cortex (17 hydroxy-11 dehydrocorticosterone, Compound E) and of a Pituitary Adrenocorticotrophic Hormone on Rheumatoid

Arthritis. Preliminary Report. *Proc. Staff Meet., Mayo Clin.*, 24:181, 1949.

OSTEO ARTHRITIS

The term osteo arthritis has numerous

varieties are encountered, the primary and secondary. The first, or primary, type is a distinctive clinical entity, an articular disease characteristically found in persons of advancing years, affecting certain joints and avoiding others, and having an extremely slow but progressive course. Primary osteo arthritis is not generally associated with marked evidences of constitutional involvement such as anemia, fever, or loss of weight. Secondary osteo arthritis is not a disease entity. Rather, it is a painful condition associated with a series of pathologic changes similar to those found in primary osteo arthritis, but supervening on a primary joint injury which has been brought about by other causes. Thus, joints which have been injured by trauma, infections, or by other articular diseases such as rheumatoid arthritis, may eventually show changes similar in character to those found in primary osteo arthritis, and may then be said to be sites of secondary osteo arthritis.

In both types, characteristic symptoms are pain on use, muscular and articular stiffness, creaking and grating. Effusions are uncommon except following accidental trauma. Affected joints may become enlarged by marginal hypertrophy but not by inflammatory exudates. Atrophy of adjacent musculature is not prominent.

Joints most frequently affected in primary osteo arthritis are terminal interphalangeal joints of the hands (Heberden's nodes), knees, cervical and lumbar spine, hips (malum coxae senilis), metatarsophalangeal joints of great toes, temporomandibular joints (Costen's syndrome), and acromioclavicular joints. Occasionally the middle row of

affected. II
carpus,
are practically never involved in this disease.

Laboratory data yield negative information in most instances of osteo arthritis.

Sedimentation rates hemoglobin values erythrocyte counts and various blood chemical determinations are generally normal in uncomplicated cases Roentgenograms characteristically show narrowing of articular spaces various degrees of spur formations sclerosis of subchondral bone plates and occasionally subchondral cysts Osteoporosis is not a feature in usual cases

Secondary osteo arthritis does not choose any special joints but appears wherever concomitant factors of previous injury and continued use are present Secondary osteo arthritis is a localized disease

Treatment Treatment for osteo arthritis should aim to alleviate symptoms and prevent progression of the underlying pathologic processes Healing of this disease can not be achieved because of the inability of cartilage to regenerate and because hypertrophied bone margins do not reabsorb

Useful measures of treatment for osteo arthritis include proper reassurance rest and physical therapy removal of traumatizing factors orthopedic procedures and medications Roentgen therapy removal of infectious foci gold therapy and hormones have not been proved of value

REASSURANCE Reassurance is a most important therapeutic measure for this condition Because symptoms of osteo arthritis often resemble those of rheumatoid arthritis these individuals commonly assume they are suffering from the more crippling rheumatoid arthritis This misconception is a cause for great anxiety in many instances and such anxiety should be relieved by thoughtful discussions between patient and physician

REST AND PHYSICAL THERAPY Progression of the pathologic phenomena resulting from use and wear can be slowed by placing affected joints at rest Two to 3 weeks of rest in bed may result in long lasting alleviation of pain in severe cases Regulated periods of rest should be planned for each day Work and traveling activities should be thoughtfully examined with a view to minimizing trauma Unnecessary weight bearing should be eliminated Obesity should be overcome with diet Abnormal postures should be corrected with well fitted supportive corsets corrective shoes or other orthopedic appliances

Measures of physical therapy worthy of

use in osteo arthritis include applications of heat and massage These regularly provide a degree of comfort although no healing effect can be demonstrated Warm baths hot water bottles infra red bulbs and hot compresses serve satisfactorily as sources of heat Massages should be given preferably by a family member who can administer the treatments daily

Exercises have no place in the treatment of osteo arthritis Associated pathologic processes do not lead to ankyloses hence there is no need for movements to prevent fusion of joints Manipulations and exercises of all types may in fact hurry the wearing processes hence should be avoided

Orthopedic procedures useful for osteo arthritis are mentioned below in connection with measures for treatment of special forms of osteo arthritis

MEDICATIONS Up to the present no definitive drug therapy for osteo arthritis has been evolved Useful medicaments however are those which relieve pain or aid in securing rest through mild sedation Aspirin 0.6 gm or sodium salicylate 0.6 gm provide comforting relief from pain in most instances although occasionally severe pain may require small doses of codeine or another narcotic

Thyroid extract vitamins iodides and colchicine are worthless

DIET Food factors beneficial for osteo arthritis have not been discovered Weight reduction diets are commonly employed for obese patients with a view to relieving the factor of excess weight

ROENTGEN THERAPY Although roentgen therapy is often employed in centers where appropriate apparatus is available this form of treatment is not of proved value for osteo arthritis Such treatments are usually rela-

intra articular injection therapies of osteo arthritis have been recorded Acid potassium phosphate lactic acid and benzyl salicylate have been recommended currently for intra articular injections but none of these has found general acceptance

HORMONES Both male and female sex hormones have been studied as treatment measures for osteo arthritis but none has stood

the test of time. Their use cannot now be justified for osteoarthritis. Cortisone and pituitary adrenocorticotropin have not yet been studied as treatment measures for osteoarthritis.

Treatment of Special Forms of Osteoarthritis. **TERMINAL INTERPHALANGEAL JOINTS (HEBERDEN'S NODES).** This most common of all forms of osteoarthritis is often asymptomatic but may cause aching, burning numbness and stinging.

Paraffin dips (see treatment of rheumatoid arthritis) and contrast baths are forms of physical therapy which can be readily employed in the home for Heberden's nodes. This condition causes less discomfort if the patient avoids sewing and other handicrafts. Eventually Heberden's nodes become painless and require no further treatment.

CERVICAL SPINE. Heat and massage with traction often provide notable relief. Radiant heat first should be applied for 30 minutes followed by massage of the neck and shoulders. Traction should then be applied to the head by means of canvas sling attached under the chin and occiput leading thence to a 4 or 6 pound weight suspended over the head of the bed. This procedure may be carried out once or twice daily. Patients with cervical osteoarthritis derive comfort from sleeping without pillows or with a single small pillow. A padded cotton bandage 4 inches in width and 2 or 3 yards in length wrapped around the neck at night for periods of an hour or two several times during the day may also provide comfort by minimizing irritative effects of constant motions.

LUMBAR OSTEOARTHRITIS. This condition may be associated with persistent lumbar backache or with repeated episodes of acute unilateral or bilateral lumbar pain. In some cases the patients suffer episodes of sciatica. Therapy during acute attacks should include rest if possible in bed on a firm mattress together with applications of heat and massages. In some instances pain may be so severe as to require temporary use of narcotics.

For more chronic symptoms of lumbar osteoarthritis supportive corsets or braces may aid in minimizing movements which aggravate symptoms. Special attention should be given to regulation of occupational and recreational activities of patients with this

condition as in some cases comfort can be maintained only by means of a restricted life program.

OSTEOARTHRITIS OF THE HIP. This condition is generally encountered in middle aged or older patients. Damage is commonly more advanced on one side than on the other but some patients have severe bilateral destruction. The problem of therapy is a difficult one. For severely painful episodes bed rest for a period of 2 or 3 weeks

walk
voided
condi

tion should be advised to seek occupations which permit their being seated for most of the day. For severe cases effects of weight bearing should be minimized with canes or crutches.

A surgical procedure worthy of consideration for some patients with osteoarthritis of the hips is cup arthroplasty. This operation involves reshaping of the femoral head and acetabular cavity followed by interposition of a metallic cup between the femur and acetabulum. The procedure is a major one and should not be undertaken in persons of advanced years with severe arteriosclerosis or other debilitating ailments.

Lesser operations including forage or drilling of the femoral neck, transplantation of the trochanters and cholecotomy (removal of spurs) have not proved to be of sufficient value to justify their regular employment. Resection of the obturator nerve is still under study.

EDWARD F. ROSENBERG

PALINDROMIC RHEUMATISM

The term "palindromic" derived from Greek roots meaning "to recur" was employed by Hippocrates to characterize erysipelas and other ailments tending to appear repeatedly in the same individual. This term was applied recently to a "new" previously unrecognized rheumatic disease the outstanding symptom of which is multiple recurring attacks of painful inflammation affecting joints and adjacent tissues.

In this disease articular attacks usually affect but one joint although in some individuals a number of joints are attacked

simultaneously Episodes appear suddenly persist but a few hours or days and disappear leaving no residual articular damage Recurrences may be experienced at irregular intervals Fewer than 100 cases have been reported to this time

Onset of the attacks may occur at any time of the day but there is a tendency for attacks to have their onset in the late afternoon Attacks sometimes appear instantaneously the overlying skin becoming suddenly distended tender and discolored Attacks may be associated with considerable disability from pain but generally little or no constitutional reaction is evident Patients do not lose weight and generally show no elevation of the sedimentation rate Fever is not a feature of the disease

In addition to involving the joints some attacks affect periarticular structures and structures which are far removed from joints

A distinctive type of intracutaneous or subcutaneous nodule occurs in palindromic rheumatism These appear suddenly generally about the hands or fingers last from a few days to 6 or 7 days and disappear completely

Röntgenographic findings in joints are characteristically normal although patients with palindromic rheumatism may show changes from other causes as for example from unrelated primary or traumatic osteoarthritis

Treatment A physician who undertakes the treatment of a patient with this bizarre disease should understand that many questions concerning it remain unanswered The

miscellaneous measures but it is not certain that improvement which they noted was always related to the treatments which were being applied For example patients have claimed relief after receiving intravenous calcium gluconate and also after institution of such psychotherapeutic measures as adopting a child or taking a vacation

Several patients with palindromic rheumatism have recently been treated with soluble gold compounds This treatment was followed by a complete arrest of articular manifestations in each of 11 patients whose cases were reported by Boland and Headley This means of treatment should be investigated further

Patients with palindromic rheumatism should be examined carefully for infected foci and if any are present they should be removed General hygienic measures should be employed including regulated rest a carefully planned well rounded diet Simplified physical therapy measures should be used d

moist lamps regions Analgesics drugs and sedatives should be administered for severe pain Unfavorable psychologic situations should be corrected wherever possible A search should be made for decided allergies and if any are found measures for their correction or elimination should be applied

If attacks persist and cause notable discomfort or disability gold therapy may be tried employing principles outlined for use of gold in the section on rheumatoid arthritis

EDWARD F ROSENBERG

REFERENCE

- Boland E W and Headley N M Treatment of So-called Palindromic Rheumatism with Gold Compounds *Ann Rheumat Dis* 7 246 1948

ARTICULAR DISEASES ASSOCIATED WITH SPECIFIC INFECTIONS

Acute suppurative arthritis results from metastasis of blood borne infections from extension of infection to joints from adjoining osteomyelitis or from penetrating wounds which enter articular cavities Treatment of patients with such bacterial infections in

some metabolic factor Remedies already tried without success include measures against allergy psychotherapy anti infectious therapy and nonspecific shock therapy Histamine desensitization epinephrine ephedrine benzedrine and the newer anti allergic drugs including benadryl and pyribenzamine have been ineffective in palindromic rheumatism Measures directed against supposed infections including removal of foci and the administration of sulfonamide penicillin and other antibiotics have also failed

Some patients have reported relief from

joints is today often the responsibility of the internist as well as of the orthopedic surgeon.

From a numerical point of view, specific forms of arthritis constitute only a small proportion of "run of the mill" rheumatism cases. Most commonly encountered among these cases are gonorrheal arthritis, tuberculous arthritis and arthritis associated with streptococcal and staphylococcal infections. Syphilis, pneumococcal infections, meningitis, brucellosis, typhoid fever, and many other systemic infections are also occasionally responsible. Infections with yeast or mold like organisms, including actinomycosis, blastomycosis, coccidioidomycosis, and histoplasmosis, are also occasionally encountered.

Pains in joints, or arthralgias (not actual bacterial invasion or arthritis) may accompany many infectious ailments. In such cases, the patients experience articular and muscular pains but suppuration does not occur. Diphtheria, influenza, smallpox, mumps, scarlet fever, measles, typhemia, and many other infectious ailments may be accompanied by such arthralgias. In such cases treatment should be directed against the underlying disease and special consideration will not be given to these problems in the present chapter.

Treatments for specific forms of arthritis differ, depending on the organism which is responsible in any given case. Only a few can receive comment here.

Gonorrheal Arthritis. Among specific forms of arthritis, gonorrheal infections still occupy an important place although this complication of gonorrhea has been decreasing steadily since the use of antibacterial drugs has become widespread.

When a diagnosis of gonorrheal arthritis has been correctly made, the arthritis may be expected to subside promptly after treatment with adequate doses of penicillin. A failure of penicillin therapy in a supposed case of gonorrheal arthritis generally reflects a mistaken diagnosis.

In addition to treatment with penicillin, bed rest, immobilization of acutely painful joints by splints or sandbags, use of analgesics and narcotics should also be employed as needed.

Daily intramuscular injections of 300,000 units of penicillin will generally suffice. The

intra articular administration of penicillin is not necessary in most instances.

If suppuration has taken place in an affected joint, single or repeated aspirations may be performed to remove pus and thus lessen lytic effects on cartilage of enzymes.

Orthral infections. In mild cases, activity may be permitted as soon as the local and systemic evidences of infection have subsided. After severe attacks, especially when purulent exudates have been in contact with articular structures for some days, weight bearing should be delayed for 10 days to 2 weeks after subsidence of the local symptoms in order to permit "hardening" of the cartilages.

Tuberculous Arthritis. The problem of therapy for tuberculous arthritis is a complex one, involving many factors. Important for consideration are the age of the patient, degree of closure of epiphyses adjacent to affected joints, location and extent of tuberculosis in other structures, and general condition of the patient. In most such cases, proper treatment requires combined efforts of orthopedists and internists. Systemic therapy, orthopedic fixations—internal or external—and recently, streptomycin therapy constitute the categories of treatment methods to be employed.

Rest in bed, high caloric diets, and heliotherapy are useful for most patients with tuberculous arthritis. Orthopedic procedures applicable to articular tuberculosis vary with the site of the lesion and are not considered here.

The role which presently available antibiotic substances may play in treatment of articular tuberculosis is not yet clearly established. Penicillin and the chemotherapeutic drugs are without effect. Earlier reports concerning effectiveness of streptomycin were pessimistic but more satisfactory results have been reported within the past year. A favorable influence on the course of tuberculous arthritis has followed use of this substance in doses of 1 gm. every 8 to 12 hours for 3 to 4 months. Toxic reactions rarely interfered with continuation of this therapy. More time will be required before

streptomycin therapy for tuberculous arthritis can be evaluated satisfactorily

Arthritis from Streptococcal or Staphylococcal Infections Infection with these organisms must be considered in the differential diagnosis in every case wherein acute articular inflammation is present. Among patients with suppurative arthritis, staphylococci have been found responsible in approximately 50 per cent of the cases, hemolytic streptococci in 25 per cent, and miscellaneous other organisms in the remainder.

Prompt and complete evacuation of infective effusions by repeated aspirations and lavage, or by means of incisions and drainage was the aim of treatment in these cases only a decade ago. Following such treatments the incidence of ankylosis and the mortality rates were high. Today ideal treatment consists of prompt bacteriologic diagnosis followed by administration of appropriate antibiotics. These measures should be supplemented by arthrotomies only if destruction is proceeding in spite of adequate antibacterial therapy.

Choice of antibacterial drugs can best be made after an accurate identification of the invading organism and where possible, after performance of appropriate antibiotic sensitivity tests. Most strains of streptococci, staphylococci, pneumococci and members of the *Clostridium* family are susceptible to penicillin. Also susceptible to penicillin are most strains of meningococci, gonococci, diphtheria organisms, *Streptobacillus moniliformis* and *Spirillum minus*, *Treponema pallidum* and *Treponema pertenue*.

For infections with gram negative bacilli streptomycin is preferable. Usually sensitive to streptomycin are organisms of the *Escherichia*, *Proteus*, *Pseudomonas*, *Shigella*, *Pasteurella*, *Klebsiella*, and *Hemophilus influenzae* groups.

Aureomycin and chloromycetin are effective against rather wide ranges of bacterial varieties, including some which are penicillin or streptomycin resistant. Reports of the use of these newer agents in articular infections have not been published; however, their employment would seem reasonable for patients in whom an organism resistant to streptomycin and to penicillin is causing the infection.

Arthritis of Actinomycosis This condition generally affects the vertebrae, is often associated with formation of discharging sinuses and may readily be mistaken for tuberculosis. Therapy thus far devised has been ineffectual and the mortality rate has been high. Sulfanilamide, iodides, roentgen rays, and penicillin have been employed without notable success.

Coccidioidal Arthritis Arthritis occurs both in the early acute or benign phases of coccidioidal infection and in the later chronic granulomatous phase of this disease. In the early acute period, articular involvement is generally transient and usually clears without leaving residual damage. Chronic granulomatous coccidioidal arthritis is often mistaken for tuberculous arthritis. This condition is serious, progressive, and destructive of bone and cartilage. Diagnosis is dependent on demonstration of the causative organism in tissues from the areas which are involved.

Specific therapy has not been devised for chronic coccidioidal infection, and as the process tends to metastasize, early recognition should call for careful consideration of amputations as possible lifesaving measures.

Histoplasmosis This condition is a chronic generalized disease caused by infection with *Histoplasma capsulatum*. Its usual manifestation is in the form of a chronic, wasting febrile illness with enlargement of the liver and spleen, anemia, and leukopenia. Pulmonary lesions, widespread skin eruptions and diffuse lymphadenopathy are frequent complications. Involvement of a knee joint has been reported in one individual. Amputation was performed in this instance.

No other effective therapy has been devised for histoplasmosis.

Meningococcal Arthritis Articular complications associated with meningococcal infections may be one of three varieties: (1) arthralgias occurring during the first few days of the infection and often appearing simultaneously with cutaneous hemorrhages; articular involvement of this period is transient, resolving without suppuration; (2) suppurative meningococcal arthritis involving usually a single joint (often a knee), this condition is associated generally with effusions of serous or seropurulent fluid; (3) arthralgias of serum sickness, this has rarely

en seen since serum therapy has been

normal for 5 days The effect of terramycin remains to be studied

EDWARD F ROSENBERG

ganisms should be tested for sensitivity to various sulfonamides and antibiotics and the patient treated with the most effective

ains
If a patient has been treated on

arterial infection of the joints

Actual invasion of joints by *Brucella* is rare, occurring perhaps in only 1 or 2 per cent of cases In such cases there may be metastatic infection associated with brucellar epicemia or extension may occur to joints from adjoining foci of brucellar osteomyelitis Almost any joint may be affected in the latter types of cases but spinal joints have been the most frequent sites of such involvement A true estimate of the value of various therapies for brucellosis is difficult because of varying courses exhibited by the disease in different individuals Not infrequently patients recover spontaneously although apparent recovery may be followed by recrudescences

Treatment of articular complications of brucellosis is essentially the problem of treating the underlying disease For this purpose combined sulfadiazine and streptomycin therapy has been most successful If suppuration ensues, incision and drainage may be required

Remarkable recoveries from brucellar arthritis following oral administration of aureomycin have been reported recently Doses employed were 0.1 gm the first day, 0.6 gm the second day, 1.6 gm the third day, and 2 gm the fourth day Thereafter the daily dose was increased to 4 or 8 gm The latter amounts were administered for 2 to 14 days

If chloromycetin is used, the initial dose should be 2 to 3 gm followed by 0.25 gm every 3 hours until the temperature has been

- Bickel W H et al. Streptomycin in Tuberculosis of Bone and Joint. *JAMA*, 137 682 1948
Key J A and Large A M. Histoplasmosis of Knee. *J Bone & Joint Surg*, 24 281, 1942

REFERENCES

INTERMITTENT HYDRARTHROSIS

This curious remitting disease of joints was first described in modern medical literature in 1831 By 1939 the number of reported cases was only 106 Thus, in more than 100 years the incidence of reported cases was approximately one each year This impression of great rarity is not justified, as, without doubt, many cases have been observed but not reported Certainly intermittent hydrarthrosis is not infrequently encountered among clients of arthritis clinics and rheumatism spas

The distinctive symptom of this condition is regularly recurring articular swellings, lasting but 4 days to a week Periods of freedom range from a few days to a month Occasionally several joints are affected

Two varieties are encountered The first has been designated "symptomatic intermittent hydrarthrosis" because the swellings are believed to be early symptoms of rheumatoid arthritis In this form attacks recur regularly for varying periods but remissions tend to disappear as attacks gradually merge into persisting articular inflammation Sometimes one or more joints other than those taking part in the recurring swelling display evidences of chronic arthritis

A second form has been called "idiopathic" because it is believed not to be a forerunner of rheumatoid arthritis

Speculations and research concerning the etiology of intermittent hydrarthrosis have not thus far led to a satisfactory conclusion The periodicity of attacks suggests an allergic reaction either to bacteria or to some other irritants However, evidence which has thus far been brought forward in support of allergy as a cause has not been impressive Patients with intermittent hydrarthrosis do not regularly suffer with other allergic symptoms such as angioneurotic edema, hives,

asthma or hay fever and usually do not respond to antiallergic measures

A case has been reported in which organisms of the brucella group were found in synovial fluid removed during an episode. However search for these and other organisms in patients studied by this writer has been unsuccessful.

An endocrine dysfunction is suggested by several patients who experienced remissions during pregnancy also because of the analogous cyclic character of menstruation.

Treatment. Results of most treatments have been disappointing. Rest in bed and administration of salicylates, aspiration of fluid and administration of streptococcal vaccines have regularly failed to bring the process to a halt. Attacks may disappear spontaneously while a patient is under observation, a consideration which makes for great difficulties in interpreting the value of any treatment measure.

During acute attacks patients are more comfortable at rest but if it is necessary for the patient to continue activity during attacks the swollen knee should be supported

Other treatment measures worthy of trial include intravenous administration of typhoid vaccine as described under rheumatoid arthritis, removal of obviously infected foci and avoidance of foods to which the patient is definitely sensitive.

In 2 instances reported by Krida a cure followed synovectomy but this operation has not prevented the appearance of a progressive arthritis (sometimes in other joints) following synovectomies performed on patients observed by this writer.

Röntgen therapy halted recurrences in one patient as recorded recently by Ragan. This patient received eight treatments each of 225 r at 25 cm distance, 2 ma intensity.

also reported the case of a patient whose attacks ceased following treatment with gold sodium thiomalate. Both measures seem worthy of trial if simpler measures fail.

Desensitization to histamine by means of intravenous and intramuscular injections has

repeatedly failed to influence the course of the disease in my patients. I no longer attempt this procedure.

Attacks have ceased following administration of ergotamine tartrate in doses of 1 mg daily given for approximately 2 months followed later by repeated courses of 1 tablet daily for periods of about a month when attacks tended to recur.

The prognosis is uncertain. In some cases regular recurrences of attacks continue for years even for two or more decades without change in symptoms. In many instances the patient eventually displays a "full blown" picture of rheumatoid arthritis.

EDWARD F. ROSENBERG

REFERENCES

- Krida, A. Intermittent Hydrarthrosis of Knee Joint. Report of 2 Cases Apparently Cured by Synovectomy Together with Pathological Findings. *J Bone & Joint Surg* 15:449 1933.
Ragan, C. Intermittent Hydroarthrosis in Connexion with Arthritis and Allied Conditions. Philadelphia: Lea & Febiger 1919.

GOUT

Gout is a metabolic disease the outstanding features of which are recurring episodes of articular inflammation later becoming chronic tophi (deposits of urate crystals in articular periarticular or subcutaneous tissues, cartilages and kidneys) and a notable tendency toward hyperuricemia.

Symptoms of gout generally progress in an orderly and developing pattern knowledge of which is essential for prompt recognition and proper treatment. For this reason special attention is given to certain general considerations before discussing treatment. The specific metabolic anomaly which lies at the basis of gout may be inherited in some and possibly in all patients with this disorder. Between the moment of acquisition and appearance of the articular phenomena a period elapses which may be designated as a larval period. During this time the patient may have no symptoms or occasionally may

Advent of articular attacks may be considered as marking the opening of the second

period of gout. During this second period patients characteristically suffer repeated attacks of acute, self limited arthritis. Such attacks may appear without premonition, have a predilection for the feet and especially for metatarsophalangeal joints of the great toe, but not infrequently affect other joints of extremities. Early attacks generally but not always remain monoarticular. Accompanying pain is variable, being moderate in some but violent in others. Such attacks last several days or at most a week or two and recur at intervals of months or years. Hyperuricemia is more frequently encountered during the

tered with increasing frequency after onset of articular attacks and a notable tendency is observed for gouty individuals to experience episodes of olecranon bursitis and renal colics from passage of uratic gravel.

After numerous and prolonged articular at-

serious crippling results from extensive damage to joints in this period.

Chronic nephritis, recurring renal colics and extensive deposits of tophaceous material in periarticular and subcutaneous tissues are characteristic complications of the third period. Tophi may assume huge proportions and destroy the overlying integument, producing sinuses through which crystalline urates and other necrotic material

g of a disturbed chemical mechanism for the handling and disposition of uric acid. This fact has been evident for more than a century and a half since Wollaston demonstrated urates in tophaceous material in 1779. The seat of this anomalous disorder has not yet been found, although recently important new facts have come to light concerning patho-

an im with ketosteroid compounds at a lower rate than nongouty individuals. In addition balance studies of electrolyte and water metabolism have disclosed evidence suggesting that acute

attacks tend to occur at times of decreased adrenal cortical activity. Also acute gouty arthritis has been terminated abruptly by administration of adrenocorticotrophic hormone (ACTH) but attacks have often reappeared within a few days after withdrawal of this hormone.

These observations suggest that the adrenal cortex plays an important role in

necessary to await further study of these phenomena to apply these observations to treatment.

Treatment. Reasonably effective therapeutic measures have been evolved for the several phases of gout. These can be expected to produce prompt and complete relief in most instances. But, success in treatment is dependent upon the establishment of a correct diagnosis, on an accurate estimate of the condition of the patient, and on the wholehearted co-operation of the patient himself.

TREATMENT DURING THE LARVAL PHASE OF GOUT. Identification of the disease during this period is most often accomplished in family members of affected patients. When the diagnosis is made, it is reasonable to recommend that the patient eat in moderation of foods containing purines, avoid alcohol, choose occupations which do not entail exposure to lead and which do not encourage excesses in eating. An incident of articular pain should call for a careful review of the situation and if it is determined that the larval period has progressed into the second period of acute articular attacks, a more in-

ACUTE GOUTY ARTHRITIS. Treatment of a patient in this phase of gout requires two sets of instructions. These should include instructions for periods between attacks and instructions for treatment of acute attacks.

Attack free Intervals. After a patient has recovered from an acute attack he enters a period when he is in danger of the next attack. The aim of treatment for this period should be to minimize progressive tendencies of the defective urate metabolism thereby reducing incidence of further attacks.

Diet To reduce the metabolic load, purine containing foods should be allowed only in moderation. Protein foods, low in purine content, including particularly milk, cheese, eggs and breads, should be substituted for meat. Bulk, vitamins, and mineral requirements are provided by vegetables and fruits. Caloric needs should be taken into account in planning this diet. Several sample menus are illustrated in the charts. On this regimen meats are permitted in carefully limited amounts and glandular meats such as sweetbreads, liver and kidneys are excluded entirely. Certain vegetables and cereals which contain notable amounts of purines are permitted only sparingly.

During attack-free intervals it is best to allow no foods containing significant amounts of purines—in other words, a purine free diet—during 2 or 3 days of each week. For the remaining days the diet is planned to be low in, but not free of purines. For the patient with gout of average severity a small serving of nonglandular meat can be allowed on 3 days of each week. Other purine containing foods should be omitted on these days. One serving of vegetable such as lima beans, spinach mushrooms, or a serving of whole grain cereals such as cooked whole wheat, wheat biscuits, or oatmeal, may be allowed on 2 additional days.

Foods permitted on this diet include refined cereals such as cream of wheat, cornflakes, and puffed rice. White or fine rye bread is used in place of whole wheat bread. Butter, cream, mayonnaise, and other fats are permitted only in moderation because of the observation that uric acid in plasma tends toward higher levels in patients who are permitted a high fat intake.

For desserts, fruits are satisfactory but if the patient is not overweight he may occasionally have icecream, tapioca, or cornstarch pudding sherbets, and ices. Desserts to be avoided include those rich in fats such as chocolate cake or pudding, spiced cake or cookies, pies, and homemade icecream.

Coffee, tea, cocoa, coca cola, and "pop" do not give rise to important quantities of uric acid and may be included in the diet if proper allowance is made for content of calories.

Medications In addition to dietary restrictions, regular weekly courses of salicylates,

75 to 90 grams (5 or 11 gm) on 3 to 5 consecutive days of each week aid in effecting excretion of urates and maintenance of lower levels of urate in serum. To prevent crystallization of urates in urine during periods of urate diuresis associated with administration of salicylates in this manner, sufficient baking soda should be given to alkalinize the urine. The specific dose to be used is determined by testing the urine with litmus paper.

To some extent at least a physician may test the degree of control which he has achieved by occasional determinations of

abnormal break down of cells, a rising level of serum urate often denotes poor cooperation on the part of the patient.

Treatment of Acute Attacks Rest for Affected Joints. When an attack appears the extremity should be placed at rest. Generally it is necessary for the patient to go to bed. The foot or arm should be elevated on pillows to minimize a tendency to swell. For all but the mildest attacks, complete rest must be continued until the attack is well controlled. Premature return to activity is not infrequently followed by recrudescence of attacks. Patients should be urged not to attempt to "walk it off."

Applications of Heat Properly prepared hot wet compresses are effective in alleviating pain. Prior to applying wet cloths, the skin should be smeared with vaseline or cold cream to prevent excessive maceration. Compresses should be generous in size, large enough to cover the affected joint and an extensive area beyond the site of the attack. A thin blanket may be wrapped about the wet compresses to reduce the speed of cooling. Compresses should be changed at intervals of 1 or 2 hours and their application should be continued until the attack is well under control. When possible, wet packs should be constantly applied for the duration of an attack through the day and night.

Colchicine At the first sign of an attack a patient should start a course of colchicine. This ancient remedy is now available in a potent form, as tablets or pills each of $\frac{1}{100}$ or $\frac{1}{50}$ gram (0.65 or 0.53 mg). A course may be defined as the number of tablets

which suffices to relieve an attack or produce diarrhea. Ordinarily one may give the patient 2 tablets to start then one every hour until a loose stool results. Patients require on the average from six to fifteen doses before diarrhea appears.

Patients with gout should have colchicine readily available and should be instructed to take the tablets immediately upon appearance of symptoms which suggest that an attack is starting.

The mechanism of colchicine's action remains obscure. When administered in amounts sufficient to produce gastrointestinal irritation no shift in level of blood uric acid can be detected nor is there any increase in rate of excretion of uric acid. The drug is nonetheless effective in spite of this failure to influence the metabolism of uric acid. One writer stated recently that "over 95 per cent of acute attacks are materially benefited by a single course." Occasional instances are encountered in which the drug fails to produce such sharp remissions and for these attacks a second or even a third course may be employed.

Diet. During attacks the diet should be purine free that is free of foods containing abundant cell nuclei. This diet should also be low in fat which favors retention of urates. Milk, cheese, eggs, cereals, vegetables and fruits constitute the chief categories of foods for this period. Vegetables which contain moderate amounts of purines should be avoided during acute attacks. These include particularly beans, peas, lentils and spinach. Coffee, tea and chocolate which do not give rise to uric acid need not be eliminated from the diet.

Other Medications. Both cinchophen and sodium salicylate cause notable lowering of serum urate levels and an increased rate of excretion of uric acid in the urine. For acute attacks sodium salicylate may be given in doses of 75 to 120 grains (5 to 8 gm) daily for the duration of the attack. In particularly severe instances when attacks persist in spite of other measures the writer uses cinchophen in doses of 0.5 gm three times daily. I know of no instance in which cinchophen hepatitis has been encountered in a gouty patient.

Narcotics. Pain of gouty arthritis is occasionally intense and may necessitate adminis-

tration of codeine 30 mg morphine 15 mg or other narcotics.

A Note Regarding Certain Provocatives of Gouty Arthritis. A wide variety of physical, occupational, pharmacologic and psychologic stimuli have been observed to provoke attacks of acute gouty arthritis in susceptible persons. These have been studied in detail

kept in mind by physicians responsible for management of patients with gout and avoidance of known provocatives must be considered an important therapeutic measure.

Among physical traumata to be avoided whenever possible are the following: (1)

radical participation in sports or hobbies; (5) certain drugs including bile salts, concentrated solutions of thiamine chloride, liver extracts (except when their use is absolutely essential for treatment of pernicious anemia) and mercurial diuretics. Patients with both diabetes mellitus requiring insulin and gout should take special care to avoid insulin reactions as these occasionally provoke acute attacks. Strong purgatives which are capable of altering fluid balance even temporarily should be avoided for the same reason.

Surgical procedures of all types may be followed by exacerbations of gouty arthritis in susceptible patients. Incidence of such

doses of 75 to 90 grains (5 or 6 gm). On the day of operation and for a week or 10 days thereafter resume the same program. If the drug cannot be taken by mouth similar amounts should be given intravenously.

The Adrenocorticotrophic Hormone in Gout. Repeated observations have shown that acute attacks of gout can be quickly overcome by administration of small amounts of this hormone. Patients so treated at the Michael Reese Hospital responded within a few hours after administration of 25 to 50 mg of potent material. A problem which remains to be

solved concerns ■ tendency for attacks to recur within a few days after withdrawal of this hormone. A practical application cannot as yet be predicted.

Treatment of the Third Phase of Gout—The Phase of Chronic Gouty Arthritis
Chronic articular deformities, large subcutaneous tophaceous deposits renal and vascular complications of the disease constitute the main problems for treatment in this period. For chronic articular deformities physical therapy procedures are occasionally of value. Applications of heat from infra red bakers, warm moist compresses for flare ups of articular inflammation, and mild stimulating massage for wasted muscles are worthy of use. When tophaceous material causes deformities which interfere with the use of

extremities, an orthopedic surgeon can, at times, greatly improve the situation by tophectomies combined with plastic restoration of damaged regions.

For cardiovascular and renal complications of chronic gout no specific measures are available. However, to the therapeutic program indicated by the particular complication should be added strict dietary precautions, together with use of purine diuretics as described above.

Some consider continuous administration

diuretic powers and may be used to supplement either salicylates or cinchophen in severe cases.

POINTS TO REMEMBER ABOUT A PURINE FREE DIET

(1) Always avoid

Alcohol	Meats	Onions
Anchovies	Fish	Peas
Brains	Fowl	Spinach
Gravy	Asparagus	Whole-grain cereals
Kidneys	Cauliflower	Malted cereals
Liver	Kidney beans	Whole grain bread
Meat extracts (juices)	Navy beans	
Sardines	Lima beans	
Sweetbreads	Mushrooms	

(2) Use in Moderation

Condiments	All fats	Rich desserts
------------	----------	---------------

(Uric acid is more readily excreted when the fat in the diet is moderately restricted.)

(3) Use two eggs or egg substitute per day

Substitutes for one egg	2 tablespoons cottage cheese
	1 inch cube cheese
	1 cup custard
	1 glass milk

(4) Choose abundantly the foods that are purine free consistent with the maintenance of normal weight

POINTS TO REMEMBER ABOUT A LOW PURINE DIET

is omitted on those days

SAMPLE MENU—PURINE FREE AND LOW PURINE—1250 CALORIES

Purine Free Diet

This gives an idea of the amount and kind of food permitted when WEIGHT REDUCTION FEATURES NEED TO BE INCLUDED IN THE DIET INSTRUCTIONS

Breakfast	Fruit fresh	1 serving
	Egg not fried	1
	Bread white (may be toasted)	1 slice
	Butter	1/2 square
	Beverage tea or coffee, as desired	
10 00 A M	1 glass unsweetened fruit juice with	
	1 beaten egg white	

<i>Dinner</i>	Eggs	2 or egg substitute
	Vegetable no purine	1 serving
	Salad (permitted foods)	1 serving
	Bread white	$\frac{1}{2}$ slice
	Dessert fresh or unsweetened fruit	1 serving
	Milk skimmed	1 glass
	Beverage tea or coffee as desired	
	3 00 P.M. 1 glass unsweetened fruit juice with 1 beaten egg	
<i>Supper</i>	Eggs	2 or egg substitute
	Vegetable no purine	1 serving
	Salad (permitted foods)	1 serving
	Bread white	$\frac{1}{2}$ slice
	Butter	1 square
	Dessert fresh or unsweetened fruit	1 serving
	Milk skimmed	1 glass
	Beverage tea or coffee as desired	
	8 00 P.M. or before retiring 1 glass of unsweetened fruit juice with 1 beaten egg white	

For adequate vitamin C include one serving of citrus fruit or tomato in some form each day
Vitamin supplement as directed

Note For the low purine diet, a non-purine vegetable may replace a purine vegetable or a whole grain bread or cereal may replace white bread or refined cereals for the meal
For that day a purine containing vegetable may replace a non-purine vegetable or a whole grain bread or cereal may replace white bread or refined cereals for the meal

SAMPLE MENU—PURINE FREE AND LOW PURINE—3500 CALORIES

Purine Free Diet

This menu shows the amount and kind of foods permitted for persons engaged in moderately active work or for less active persons who need to gain weight

<i>Breakfast</i>	Fruit	1 serving
	Cereal no whole grain	1 serving
	Egg not fried	1 or egg substitute
	Bread white may be toasted	1 slice
	Butter	1 square
	Cream coffee	2 tablespoons
	Milk for cereal	1 glass
	Beverage tea or coffee as desired	
	Jelly or preserves	1 tablespoon
	Sugar	
	10 00 A.M. 1 glass sweetened fruit juice	
<i>Dinner</i>	Soup if made from allowed milk and vegetable	1 serving
	Eggs	2 or egg substitute
	Potato or substitutes not fried	1 serving
	Vegetable no purine	1 serving
	Salad (permitted foods)	1 serving
	Bread white	$\frac{1}{2}$ slice
	Butter	1 square
	Dessert fruit or simple dessert	1 serving
	Milk	1 glass
	Beverage tea or coffee as desired	
	Jelly or preserves	
	3 00 P.M. 1 glass sweetened fruit juice	



SAMPLE MENU—PURINE FREE AND LOW PURINE—2500 CALORIES—(Continued)

<i>Supper</i>	Eggs	2 or egg substitute
	Potato or substitute not fried	1 serving
	Vegetable no purine	1 serving
	Salad (permitted foods)	1 serving
	Bread white	2 slices
	Butter	1 square
	Dessert fruit	1 serving
	Milk	1 glass
	Beverage tea or coffee as desired	
	Jelly or preserves	1 tablespoon
	8:00 P.M. or before retiring—1 glass sweetened fruit juice	

For adequate vitamin C include 1 serving of citrus fruit or tomato in some form each day
Vitamin Supplement as directed

Note For the low purine diet the same general suggestions should be followed with the

EDWARD F. ROSENBERG

REFERENCES

- Hench P S Diagnosis and Treatment of Gout and Gouty Arthritis JAMA 116:453 1941
Wollaston W H On Gouty and Urinary Concretions *Philosoph Trans Roy Soc London* 18 213 1797

FIBROSITIS

Among patients of rheumatism clinics and arthritis centers a large proportion complain of a distinctive group of symptoms involving muscular and articular aching and stiffness, yet these patients do not show evidence of inflammatory or degenerative damage to joints or muscles. The term fibrositis has been assigned to this syndrome for want of a better designation.

In terms of this concept, fibrositis is defined as a clinical syndrome (not a pathologic entity) acute, subacute or chronic, apparently involving subcutaneous tissues, fibrous origins, insertions and aponeuroses of muscles, articular capsules, ligaments, tendons and possibly encapsulating membranes of nerves. Characteristic symptoms are pain and stiffness aggravated by inactivity, partially relieved by exercise, use, applications of heat, massage or simple analgesic drugs such as aspirin. These symptoms are often aggravated in anticipation of changing weather, and are made worse by excessive use, profound psychic disturbances and by systemic infections such as colds or influenza.

Aside from an important necessity to distinguish fibrositis from chronic arthritis it is also important to separate this condition from the commonly occurring form of psychoneurosis which manifests itself especially in complaints of pain in muscles and joints. The latter distinction is usually de-

especially difficult when patients with fibrositis show evidences of psychoneurosis also. As in all diseases, the physician must often deal both with organic and psychic disturbances in the same individual.

Fibrositis may be classified not only in terms of its acuteness but also according to location. Thus, a physician may expect to encounter certain distribution patterns in patients with this disease. Symptoms may be mainly intramuscular, as in wryneck or lumbago. Symptoms may be largely confined to regions about joints as about the small joints of the hands, about the knees or about a shoulder. Tendons and fasciae are predominant sites of involvement in some cases, as for example in Dupuytren's contracture of palmar fasciae in tennis elbow, and in plantar fasciitis. Rarely, sheaths of nerves are seemingly involved with resulting neuritis-like symptoms.

Superimposed on various other ailments including rheumatoid arthritis, rheumatic fever, gouty arthritis, and many generalized

DISEASES OF THE LOCOMOTOR SYSTEM

fections some patients have symptoms indistinguishable from those of primary fibrositis. For this situation the term secondary fibrositis seems justifiable. A treatment for these secondary forms of fibrositis is usually a matter of proper treatment for the underlying disease. In the discussion on treatment which follows only primary fibrositis will be considered.

Treatment Having established a diagnosis of primary fibrositis the physician must usually take time to explain the nature of this ailment to the patient. In this condition as in osteo arthritis many patients suspect the worst assuming they are afflicted with a deforming disease. Often assurance is the only measure of treatment needed and when properly assured many patients tolerate fibrositis philosophically without systematic therapy.

Definitive therapy of fibrositis has not been evolved. The etiology of this condition remains unknown and developing knowledge of hormone therapy for rheumatoid arthritis has not yet progressed to a point where relationship to fibrositic conditions can be discerned. Under present circumstances therefore treatment remains empiric but reasonably satisfactory measures have been evolved through years of patient clinical observation.

Useful measures include regulation of rest physical therapy analgesics removal of infected foci and for some patients foreign protein therapy.

Employment of rest should be patterned to the intensity of symptoms. For violent acute episodes as in acute torticollis lumbago or acutely painful shoulder affected parts should temporarily be placed at complete rest. For chronic intramuscular fibrositis accompanying fatigue generally dictates regular periods of midday rest combined with extra hours of rest in bed at night.

Physical therapy procedures worthy of use are preferably simple measures capable of employment in the home. These include warm baths electric pads simple electrical bakers or infra red bulbs. Local heating is often especially comforting if followed by a few minutes of firm massage.

Occasionally patients derive additional comfort from physical therapy administered by trained technicians. For usual cases home

measures suffice if supplemented by professional treatments once or twice weekly.

FOCAL INFECTION Comments on focal infection in relation to rheumatoid arthritis may be applied to fibrositis. In general it seems reasonable to suggest removal only of obviously infected foci.

Aspirin or sodium salicylate are the most efficient of the analgesic drugs. These are administered in dosage of 10 grains (0.6 gm) every 3 to 4 hours as necessary for pain or discomfort. Patients need to be assured that continued occasional use of salicylates is without harmful effect. Rarely violent episodes of shoulder pain or lumbago require codeine or other narcotics.

Employment of local anesthetic injections into "trigger zones" is popular in some clinics. Five or 10 cc of 1 per cent procaine solution may be injected into painful regions without harmful effect. For some patients this procedure seems to provide a degree of relief although the relief is rarely maintained. This procedure has been employed particularly in treatment of acute episodes as for example in patients with acutely painful shoulder.

Röntgen therapy vitamins particular dietary factors curare like drugs and various hormones have been employed but proof of their effectiveness is lacking and none are recommended.

Symptoms of fibrositis have been relieved during pregnancy and during episodes of jaundice. It is to be hoped therefore the development of knowledge concerning steroids and other forms of hormone therapy may prove their value in the treatment of fibrositis.

EDWARD F. ROSENBERG

OSTEITIS DEFORMANS (Paget's Disease of the Bone)

Although James Paget first described bone disease that bears his name in 1877 we still have no clear concept of its cause. It is a form of fibrous dysplasia of bone is a localized disease and is never generalized. It may involve one bone (monostotic) or many (polyostotic form). The most frequently involved bones are the sacrum femur cranium sternum pelvis tibia ribs and humerus in that order.

occurs almost exclusively after 40 years of age, but has been described in patients as young as 21 years

At present there is no effective treatment of the essential lesion of this disease, so that we are reduced to treating its complications

Pain Probably in the majority of patients with Paget's disease the condition is entirely asymptomatic and the diagnosis is made in the process of roentgen examination of the bones for other causes. However, in other patients "bone pain" may be the presenting and very troublesome complaint. At times pain in an extremity may be due to inadequate circulation because of associated arteriosclerosis. This association of arteriosclerosis and Paget's disease of the bone is so common that some writers have assumed an etiologic factor to be present.

Gill and Stein recommend the use of calcium carbonate by mouth 4 gm of the powder being given two or three times daily, unless the stools become loose in which case the amount is decreased. A diet low in calcium is also recommended. Newman in reporting a statistical study of 82 cases, states that 6 of 8 patients so treated show symptomatic improvement within 1 to 2 months while on this therapeutic regime, but symptoms promptly recur when they are taken off it.

Roentgen therapy has been used on an empiric basis for relief of pain and does seem to be of some value. A few hundred roentgen units are given over the painful area as in the treatment of chronic inflammation with this means. There is no proof that roentgen therapy causes malignant degeneration in the involved bone. Osteogenic sarcoma was formerly believed to occur in 7 per cent of cases. This figure is now held to be much too high.

Fractures Fractures of weight bearing bones are prone to occur owing to the weakened condition and are almost always transverse fractures. Not infrequently a "fatigue fracture" develops. This appears on the roentgenogram as a transverse radiolucent zone at the site of greatest strain (usually the area of the apex of the bow in the bent long bone) on the convex side. At first the fracture is incomplete and resembles the "march fracture," or the fracture seen in

marked osteomalacia described by Milkman, it may go on to completion, usually, however, without great displacement of the parts. These fractures as a rule heal readily in the usual length of time and with abundant callus. Special emphasis should be placed on keeping the patient ambulatory if at all possible. When a fracture occurs in a bone involved in Paget's disease, a stimulus for bone production by the stress and strain of normal use is removed, but the destructive process continues unabated. This may lead to a hypercalcaemia and a hypercalciuria if the amount of calcium to be excreted exceeds the ability of the kidneys to excrete it or if the kidney function becomes impaired from hypercalciuria. If it becomes necessary to immobilize the patient with fracture complicated Paget's disease the blood calcium level should be watched, fluids forced and a diet low in calcium given.

Cranial Nerve Injury Loss of hearing and m...

ear in the disease process, rather than to a compression of the auditory nerve, Roentgen therapy may relieve the tinnitus and dizziness.

Kyphosis The bodies of the spine are frequently involved and a gradual deformity develops as a result of wedging compression of the softened bone. This process of wedging occurs so gradually, like the bowing of long bones that no fracture can be said to occur, and the process is not particularly painful.

Stasis Ulcers When Paget's disease involves the tibia, it may become so enlarged that the circulation, especially the venous return of blood, is interfered with, and stasis ulcers develop. These are best handled by the application of Unna's paste boot. A section of the boot, approximately two or three times the diameter of the ulcer, is then removed to permit the application of wet dressings to the ulcer. We prefer to use several flats soaked with a tyrothricin solution and applied under moderate pressure from an elastic bandage as the wetting and antiseptic agent. The dressing should be changed infrequently.

VERNON C. TURNER

REFERENCES

- Albright F and Reifenstein H C *The Parathyroid Glands and Metabolic Bone Disease Selected Studies* Baltimore Williams & Wilkins Company 1948
- Ell A H and Stein I *Bone Metabolism Its Principles and Relations to Orthopaedic Surgery J Bone & Joint Surg* 18 911 1936
- Milkman, L. A. Multiple Spontaneous Idiopathic Symmetrical Fractures *Am J Roentgenol* 30 677 1934
- Newman F W *Pagets Disease Statistical Study of 80 Cases J Bone & Joint Surg* 23 798 1946
- Paget J *Med Clin Transact* 50 37 1876
- Snapper I *Medical Clinics on Bone Diseases A Text and Atlas* New York Interscience Publishers Inc 1943

OSTEOPOROSIS

Osteoporosis is a condition in which there is reduction of the bone mass in the body it is characterized by a lack of osteoblastic activity

Osteoporosis occurs in the following clinical conditions

- (1) Disuse atrophy
 - (2) Senile osteoporosis usually a result of several factors physical activity decreases with age so that the need for bone is less a state of chronic malnutrition may occur where the protein requirements of metabolism are not fulfilled in addition the anabolic processes in the body generally are diminished in old age and bone tissue like other tissues (hair skin muscle etc) atrophy
 - (3) Malnutrition There are insufficient protein building blocks which the osteoblasts may convert into osteoids In osteoporosis the fault is with tissue metabolism as distinguished from calcium metabolism
 - (4) Cushing's Syndrome It is believed that in this condition there is an excess of adrenal cortical "sugar" hormones which inhibit the metabolism of protoplasm in general including the anabolism of osteoid
- It has been postulated that the adrenal cortex produces a "sugar hormone" and a "nitrogen hormone" that the S hormone is antianabolic and that the N hormone is like testosterone and neutralizes the S hormone that in Cushing's syndrome there is an ex-

cess of S hormone Clinically it was found that testosterone propionate in a dosage of 25 mg daily had a markedly beneficial effect on the nitrogen phosphorus and calcium balance of these patients

(5) Postmenopausal osteoporosis is the commonest of all forms of osteoporosis and is due to the deficiency in estrogen production with attendant lack of stimulation of osteoblastic activity The osteoporosis involves chiefly the spine and to a lesser degree the pelvis and skull It usually does not occur before the middle 50's but where artificial menopause has been produced it may occur at a much earlier age

Albright recommends the use of both estrogen and androgen in the treatment of senile and postmenopausal osteoporosis and gives the following dosage

Estrogens Diethyl stilbesterol 0.5 to 1

muscularly estradiol dipropionate 5 mg weekly intramuscularly

Androgens Methyltestosterone 10 to 20 mg daily orally or testosterone 50 mg

should be interrupted for 1 to 2 weeks each 4 to 6 weeks since estrogenic therapy may lead to development of cancer if the uterus

be investigated further

There are numerous drawbacks to the administration of sex hormones in the treatment of senile osteoporosis and the writer is not entirely convinced of their necessity Hormonal treatment is expensive for the patient The treatment must be continued over long periods of time and even then it has been difficult to produce undisputed roentgenographic evidence that the bones have become more calcified than before the therapy was instituted Testosterone compounds must be handled with care because of the masculinizing effect Most women will not tolerate more than 300 mg of androgen a month Steroid therapy may cause sodium retention and an elderly patient may develop edema especially if the serum pro-

tein level is low. It may be necessary to use a low salt diet and to give ammonium chloride. The writer has reported his experiences in the treatment of a large series of compression fractures of the spine, many of which occurred in elderly people with senile osteoporosis. Most of these patients were treated without estrogen therapy and made good functional recovery.

Orthopedic Management. It is important that long periods of immobilization or bed rest be avoided in these patients; otherwise disuse atrophy of bone is accentuated. Many persons with senile osteoporosis, with or without the complication of compression fracture, may be treated as ambulatory patients. The back may be strapped with adhesive tape for 2 or 3 weeks, followed by the wearing of a simple well-boned corset. Several brief rest periods on a firm flat bed and physiotherapy consisting of active exercise and postural training are given. If spinal fracture is superimposed on the osteoporosis, hospitalization for 10 to 20 days is usually necessary. Muscle spasm is relieved by hot compresses and by uninterrupted rest, or possibly by traction (bilateral Russell). Frequent passive change of position ("all in one piece") is insisted on, as well as active use of the arms and legs, even in the acutely painful stage. Within a few days the pain on movement disappears; the patient is started on gentle active postural exercises fitted with a high front laced corset and resumes normal activities.

VERNON C. TURNER

REFERENCES

- A Albright F: The Effect of Hormones on Osteogenesis in Man. In *Recent Progress in Hormone Research*, Volume 1, 1947.
 Reifstein E C Jr and Albright F: Metabolic Effects of Steroid Hormones in Osteoporosis. *J Clin Investigation* 26:24, 1947.
 Turner V C and Mead N C: Compression Fractures of the Dorsal and Lumbar Spine in Elderly People. *S Clin North America*, pp 195-205, 1949.

OSTEOMALACIA

Osteomalacia is a disorder of the skeleton in which bone matrix or osteoid is not promptly and properly calcified. In this condition there is nothing wrong with the

process of the manufacture of osteoid; the fault lies in its calcification and in this it differs in its pathologic physiology from osteoporosis and from osteitis fibrosa due to hyperparathyroidism, which are characterized respectively by poor production of bone and by too rapid destruction of bone.

Osteoid is produced by action of the osteoblasts and these are stimulated to activity chiefly by the stress and strain of use. The calcium ions are absorbed from the acid chyle of the upper intestinal tract and deposited where needed in the skeleton, probably largely through the action of the enzyme alkaline phosphatase. The action of vitamin D is twofold: (1) to aid in the absorption of the calcium ion through the gut wall; (2) to increase the excretion of phosphorus into the urine. This second action is the same as the action of the parathyroid hormone and is of importance only when excessive dosage of vitamin D is present.

Osteomalacia may be due to one or more of the following causes:

- (1) Insufficient intake of calcium
- (2) Adequate intake but inadequate absorption
 - (a) simple lack of vitamin D
 - (b) resistance to vitamin D
 - (c) steatorrhea
 - (d) achlorhydria
- (3) Adequate absorption but inadequate deposition into the matrix
 - (a) renal acidosis
 - (b) idiopathic hypercalciuria

The Food and Nutrition Board of the National Research Council recommends 0.8 gm of calcium per day for an adult man or woman. A half pint of milk (240 cc) furnishes 0.27 gm of calcium, most of which is available for absorption. A half pint of plain icecream furnishes slightly less calcium. A half ounce of cheese furnishes 0.25 gm of calcium. Green and leafy vegetables

contain from 15 to 2 gm per day. Children require from 1 to 1.5 gm.

Osteomalacia due to simple lack of vitamin D is probably rarely seen in the United States. Osteomalacia in children (rickets) in its mildest form at least is quite common.

This condition will respond to the usual small doses of vitamin D

Some individuals apparently develop a resistance to vitamin D, so that the minimum daily requirement for adequate calcium absorption (400 international units) may be totally inadequate and tremendous doses of 100 000 to 300 000 units a day may be necessary to achieve the desired results

Steatorrhea is present in children with celiac disease and in adults with chronic pancreatitis sprue and in the insufficiency of the small intestine following certain short circuiting operations on the bowel If there is a fecal fat content of 10 per cent of the fat intake steatorrhea is said to be present Steatorrhea results in an osteomalacia inasmuch as the fat soluble vitamins including vitamin D, are dissolved in the fat and passed through the intestine unabsorbed A low fat diet should be prescribed with vitamins given between meals so that they will not dissolve in the intestinal tract or an injectable form of vitamin D may be given It must be remembered that all the fat soluble vitamins must be provided (D K A and E as alpha tocopherol) for in steatorrhea both the vitamin K and the vitamin A levels may be low with increased bleeding time as well as a low serum carotinoid

Theoretically, an achlorhydria will also result in inadequate absorption of calcium since the calcium salts are soluble in acid media but insoluble in alkaline media However at this time we have no certain knowledge that the administration of hydrochloric acid in the achlorhydric animal is of value in the treatment of osteomalacia

When osteomalacia is associated with renal acidosis resulting from tubular insufficiency without glomerular insufficiency calcium appears in the urine in increased amounts This causes the serum calcium to fall which in turn results in parathyroid hyperplasia increase in excretion of phosphorus and a hypophosphatemia A demineralization of bone in this instance is treated

The patient takes from 50 to 100 cc of this mixture daily, depending on the amount needed to overcome acidosis The citric acid helps to acidify the gastric content but is burned after absorption

Renal rickets is not the same condition as renal acidosis due to tubular insufficiency In renal rickets there is an associated glomerular insufficiency, and the acidosis is due not only to the excretion of the base but also to the retention of the acid radicals and is not immediately corrected by giving base Renal rickets is not an osteomalacia but rather an osteitis fibrosis cystica generalisata since the emphasis is on bone destruction rather than on lack of calcification of new osteoid

VERNON C TURNER

REFERENCES

- Albright, F et al Osteomalacia and Late Rickets Various Etiologies Met with in United States with Emphasis on That Resulting from Specific Form of Renal Acidosis Therapeutic Indication for each Etiological Subgroup and Relationship Between Osteomalacia and Milkman's Syndrome *Medicine* 25 399 1946
Cooper L F Barber E M and Mitchell H S *Nutrition in Health and Disease for Nurses* 2nd Ed Philadelphia J B Lippincott 1928 1947 Reprint and Circular Series #122 Washington D C 1945

MYASTHENIA GRAVIS

In general the recognition of myasthenia gravis is not difficult if one keeps in mind that the first manifestations are usually the characteristic fatigability following minor exertion and the muscular weakness increasing with effort and diminishing with rest and that these are sometimes only to be seen in the external ocular muscles and

General muscular weakness of the extremities neck and trunk commonly show up only in the later stages, and only exceptionally does one see a patient in whom a particularly exhausting muscular effort has precipitated a myasthenic reaction as the first evidence of the disease Such a manifestation was once noted by the writer in the leg muscles of a young girl after her first

tion of alkali to decrease the loss of calcium in the urine Fuller Albright et al recommend a solution of 140 gm of citric acid and 98 gm of sodium citrate in 1000 cc of water

tiring bicycle excursion. The history of most patients shows that abnormal muscular fatigue occurs before loss of power. Once the disease is established, muscles with normal power at the beginning of effort become incapable of sustained contraction with continued effort. In the early stages or in the mild form of the disease, the more or less normal muscle is not affected.

visible features of the functional paralysis, the variability of the muscular strength is characteristic, as is also the unpredictability of its course. In untreated patients under 25 years of age, the prognosis is regarded as most serious, and formerly these young people died in 1 or 2 years. On the other hand, young patients in early stages of the disease may have the best and longest spontaneous remissions, such remissions having been observed up to 20 years or more.

Doubtful cases of myasthenia gravis may be recognized by employing the therapeutically effective prostigmine (neostigmine) as a diagnostic test. Viets and Schwab's combined mixture of 15 mg of neostigmine methylsulfate with 0.6 mg of atropine sulfate in a single ampule given intramuscularly is now generally used for this purpose, but we have found the intravenous administration of 0.5 mg of neostigmine methylsulfate preferable. The nature of the disease is still obscure. A deficit of acetylcholine at the nerve terminals or a decreased acetylcholine synthesis (Torda and Wolff), increased destruction of acetylcholine by a surplus of cholinesterase, the continuous presence at the motor end plates of a paralyzing agent of curare-like nature, or its gradual accumulation during muscle action leading to a raised threshold of muscle fiber excitability, a disturbance of potassium metabolism, are all possible etiologic factors (A. Schweitzer).

Drug Therapy. In spite of the great progress made since Mary Walker (1935) first showed the dramatic effect of prostigmine on myasthenic musculature, the treatment of myasthenia gravis is still symptomatic, and no cure is known. In fact, the very mode of action of prostigmine is still debated and the possibility of its acting directly on myasthenic muscles by a hitherto unknown

mechanism will have to be seriously considered. Thus the basis for the use of prostigmine as an antidote of curare, the poisoning effect of which resembles the myasthenic state, is possibly less solid than was generally thought.

However, prostigmine (neostigmine) is the drug of choice to combat the muscular weakness in myasthenia. It is used most often as prostigmine bromide in 15 mg tablets for oral administration, and as prostigmine methylsulfate in 0.5 mg ampules for intramuscular injection. Every patient presents his own therapeutic problem and the success or failure of the treatment depends greatly on the optimal cooperation of patient and physician. Lack of intelligent understanding on the part of the patient as to the purpose and limitations of the treatment is as detrimental to therapeutic success as failure on the part of the physician to determine the proper type and dosage. The patient should be informed of the substitutional character of the treatment, which varying from case to case, will overcome, or at least alleviate, his muscular weakness and enable him to enjoy his life as much as possible. In many instances it will be necessary to induce him to make certain changes in his occupation if it becomes obvious that the amount of physical effort required for his job cannot be met even with the muscular

shown that 50 per cent of such patients can live a normal life when properly treated, and that 10 per cent can do this without any restrictions. Even the more severe cases will derive comfort from the statement that remissions, sometimes of years, are by no means rare.

It is desirable to evaluate the required prostigmine dosage by hospitalizing the patient for a week, thus enabling both doctor and patient to gain useful information during the therapeutic testing period. It is recommended that observation be made as to the strength of the onset of normal activity that can be gained by an intravenous injection of 0.5 mg or an intramuscular injection of 15 mg prostigmine methylsul-

fate. By this procedure the patient comes to understand how much benefit he can derive from the treatment and will be able to state whether the effect of consecutive treatment with prostigmine by mouth equals that by injection. The administration of 0.5 mg. prostigmine intramuscularly is about the same as that of 15 mg. orally.

Well worth consideration is H. R. Viets' idea of supplying every patient, no matter how mild his disease, with ampules of prostigmine methylsulfate along with instructions for emergency injections. Likewise commendable is providing the patient with written information as to the necessary treatment for any physician or nurse who may be called in an emergency, particularly in the case of respiratory difficulties. Such

his condition—excellent, good, fair, poor, bad—on a chart four times daily. Viets' suggestion not to change the schedule in the average case without an observation period of at least 2 weeks should be followed. Before any unusual demand on his strength, the patient will do well to supplement his medication by taking an extra amount of prostigmine corresponding to that of his "before meal" dose, especially if this irregular effort occurs toward the close of day. Night medication is required if the patient complains of nightly respiratory embarrassment or of early

emergencies with sleep, which would be resorted to with a delay of about 2 to 3 hours.

Severe cases of myasthenia range from those in which oral medication cannot overcome the dysphagia sufficiently to prevent choking and aspiration of food to those in which respiratory failure is a constant danger to the frequently bedridden patient. Treatment of severe dysphagia consists first in attempting to change the usual three meals a day to five to restrict mastication to a minimum by using a soft diet, and possibly to replace the oral administration of prostigmine with a nasal catheter.

a nasal catheter will have to be instituted. Respiratory disturbances may come on suddenly and are often preceded by anxiety states, which although relieved by prostigmine methylsulfate (15 mg.), indicate threatening respiratory failure (Eaton). Such conditions may be controlled by hourly doses of prostigmine methylsulfate. Viets has given 15 to 30 mg. of this drug in 5 per cent dextrose by intravenous drip for a period of more than an hour. The use of a respirator combined with oxygen can help save the life of such a patient. Obstruction of the airway may necessitate a tracheotomy. The anxiety and the undesirable motor restlessness call for sedation. It stands to reason that all severe cases of myasthenia should be at complete rest. Even so, the amount of medication necessary may be the multiple of that used in average cases. Daily administration of 20 to 30 doses by mouth, frequently replaced by injections, may be needed, even

The average case of myasthenia gravis will be able to maintain comfort with 6 to 9 tablets of prostigmine daily and exceptionally mild cases may get along quite satisfactorily with the use of 2 or 3. The outstanding fatigue and weakness of the muscles used in swallowing indicate medication about 45 minutes before each of the three meals, thus assuring the usual intervals necessary for optimal effect. Prostigmine is much more potent on an empty than on a full stomach, but also is more likely to produce unpleasant reactions such as anorexia, epigastric distress, intestinal cramps, nausea, diarrhea and even fainting spells. In order to avoid many of these toxic stimulations of the smooth musculature, Eaton gave his patients a glass of milk and some crackers 15 minutes before the prostigmine. Atropine

side effects of the drug. An added complication is the ambulatory patient, who during his hospital observation may have been satisfied with 2 tablets of prostigmine before meals, but who will often need readjustment or increase of medication once he is on his own. The physician may obtain considerable help by adopting Schwab and Slogland's method of evaluating the effect of treatment by requesting the patient to keep score of

for periods of months and can still be followed by at least a partial remission. However certain muscles particularly the external ocular muscles and the levator palpebrae may remain more or less inactive even where prostigmine has helped the patient to a comfortable existence.

Other drugs for the relief of muscular weakness in myasthenia are of minor importance. Ephedrine sulfate which is only about 10 or 15 per cent as effective as prostigmine (Viets) may be given exclusively in mild cases two or three times daily in doses of 24 mg or less but administration should not be later than mid afternoon so as not to disturb the patient's sleep. Quite a few patients like this drug and combine it effectively with prostigmine. Potassium chloride has been found by physiologic experiments to have great influence on the transmission of nerve impulses to muscle but its use is only rarely indicated. It helps only a few and when given in sufficient doses (10 gm three times daily by mouth) its side effects are unpleasant. Guanidine hydrochloride usually given three or four times daily up to a total dose of 10 to 25 mg per kilogram of body weight (Richter) may have a satisfactory effect on muscle fatigue but here again the drug has such unpleasant side effects that most patients prefer prostigmine. Gastrointestinal disturbances can be neutralized by atropine, hyocine or belladonna but most patients interrupt this medication because of the disagreeable paresthesias around the mouth and at the finger tips, the muscle twitchings and general nervousness although alleviated by calcium gluconate. *Diisopropyl fluorophosphate* has been tried lately by Comroe and

larger doses produce unpleasant reactions on the part of the nervous system. *Amino acid (amigen)* has been given by Torda and Wolff in combination with prostigmine and found effective. Its practical use in critical prostigmine resistant conditions has yet to be worked out.

Thymus Therapy Although the role played by the thymus gland in myasthenia gravis is obscure, tumors of the thymus (15 per cent according to Good) as well as

thymic abnormalities have been found in such a high percentage of cases (50 per cent according to Gillespie) that there is no doubt that the function or dysfunction of the thymus affects sustained muscle contraction. Adams and Allan suppose that the mere presence of the thymus may be responsible for the myasthenia in sensitized individuals. Thymomas usually benign are found much less frequently than hyperplasias which resemble hyperplastic lymphoid tissue similar to the findings in a toxic thyroid gland (Keynes, Collins and Martin). The size of the thymus varying from 3 to 30 gm has been shown to have no relation to the severity of the disease (Keynes). Treatment with thymus extract has no specific effect.

Thymectomy has been done since 1908 when Sauerbruch performed the first operation of this kind. Adams and Allan have recently computed the results of 129 operated cases and found that 17 patients recovered

all or had died. This would mean that 15 per cent were significantly benefited by thymectomy. Blalock and his co-workers as well as Keynes call the results of the operative treatment encouraging.

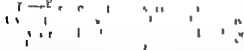
Since the operative risk is about twice the actual age of the patient (Adams and Allan) the selection of cases for operation is certainly a responsible task. The risk is due partly to the difficulty of the operation itself especially in the presence of a tumor and partly to the character of the disease which with its threat to respiratory failure would make any major operation extremely hazardous. It is felt that patients with mild cases and patients beyond the age of 35 or 40 should not be operated on. The presence of respiratory difficulties is a contraindication to the operation but once these are overcome and a remission of several months has been established by prostigmine and rest therapy, such difficulties may not exclude the patient from surgery. Every severe case of myasthenia in a young person should be treated with prostigmine in an optimal manner for several months before thymectomy is considered. Even then the possibility of spontaneous remission will raise doubts as

to the advisability of surgery. The degree of the patient's lasting disability will weigh the scale in favor of thymectomy.

As shown in the above figures the clinical results of the operation indicate that the majority of patients operated on still need medical care which means that cure is not established. Thymectomy for a thymoma verified by roentgen ray but without myasthenia gravis signs should be viewed with great reserve even though Murray and McDonald have stated that almost all patients with thymoma eventually develop myasthenia gravis.

Irradiation of the thymus whether the gland is visibly enlarged or not, is still more difficult to evaluate as to success than thymectomy. Eaton states that of 100 cases only 18 showed a remission during the ensuing 12 months. But this statistical evidence may be misleading because as Eaton says cases too ill for an operation were included and the amount of roentgen irradiation given was often insufficient. Anna Hamann the well known radiotherapist, gives her experience with irradiation of the thymus as follows:

In a small number of patients with myasthenia gravis encouraging results have been reported after roentgen and radium irradiation to the thymus gland.



thymic carcinoma is radioresistant and myxosarcoma is of moderate radiosensitivity.

If the malignant nature of a thymus tumor is verified, intensive radiation with a total dose of 5000 r or more within the tumor is indicated. Though thymic enlargement caused by lymphosarcoma may completely disappear after a small dose of a few hundred r only, the high total dose is necessary for a lasting effect.

Thymus hypertrophy may regress after small doses in the order of 600 to 800 r tissue dose in the thymus. Therefore in patients with myasthenia gravis without demonstrable thymic enlargement or in cases with enlargement of

to 500 r. Two anterior chest portals are sufficient for moderate total dosage in the thymus while for high dosage in malignant tumors cross fire from additional posterior chest portals and supraclavicular portals is necessary.

In lesions of moderate radiosensitivity regression of thymic enlargement and improvement of the muscular symptoms may be observed after 2 or 3 months only. Improvement of muscular symptoms has been reported with and without demonstrable change in the thymus. Adequate irradiation does not interfere with later surgery.

While radiation therapy is in the hands of an experienced radiologist is without risk, it has to be known that highly radiosensitive tumors may react with increased, potentially dangerous, swelling to excessive daily irradiation doses.

There is evidence that in patients in whom thymectomy is contraindicated judicious irradiation by an experienced radiologist may be a worth-while procedure.

Drug Contraindications First of the drugs to be avoided in myasthenia gravis is curare the effect of which on muscular contraction resembles the underlying pathology of myasthenia. Patients selected for curare treatment, whether in combination with shock therapy or for muscular spasticity, should first be tested for curare sensitivity. Bennett and Cash have shown that $\frac{1}{10}$ th to $\frac{1}{20}$ th of the average curare dose may precipitate muscular weakness even when given to non myasthenic patients and may cause possible respiratory difficulties in patients with a latent myasthenic condition. Thyroid medication increases myasthenic symptoms and signs and is of no help even in patients with a low basal metabolism. Eaton reports that, although hyperthyroidism complicated 6 per cent of his myasthenic patients, thyroidectomy and the use of thiouracil were not beneficial in the average case. Quinine is known to increase muscular weakness in myasthenia, and therefore a myasthenic patient with malaria should be given atabrine or some related drug that has no effect on myasthenia.

FREDERICK HULLER

REFERENCES

- Adams, R., and Allan, F. V. Thymectomy in Treatment of Myasthenia Gravis. *Dis. of Chest* 13: 436 1947.
 Allan, F. V. Myasthenia Gravis. *Lancet Clin. Bull.*, 11: 1940.
 Bennett, A. E., and Cash, P. T. Myasthenia Gravis

given at intervals of two to three months are safe.

Roentgen therapy is administered as fractionated irradiation with daily surface doses of 900

for periods of months and can still be followed by at least a partial remission. However certain muscles particularly the external ocular muscles and the levator palpebrae may remain more or less inactive even where prostigmine has helped the patient to a comfortable existence.

Other drugs for the relief of muscular weakness in myasthenia are of minor importance. Ephedrine sulfate which is only about 10 or 15 per cent as effective as prostigmine (Viets) may be given exclusively in mild cases two or three times daily in doses of 24 mg or less but administration should not be later than mid afternoon so as not to disturb the patient's sleep. Quite a few patients like this drug and combine it effectively with prostigmine. Potassium chloride has been found by physiologic experiments to have great influence on the transmission of nerve impulses to muscle but its use is only rarely indicated. It helps only a few and when given in sufficient doses (10 gm three times daily by mouth) its side effects are unpleasant. Guanidine hydrochloride usually given three or four times daily up to a total dose of 10 to 25 mg per kilogram of body weight (Richter) may have a satisfactory effect on muscle fatigue but here again the drug has such unpleasant side effects that most patients prefer prostigmine. Gastro intestinal disturbances can be neutralized by atropine, hyocine or belladonna but most patients interrupt this medication because of the disagreeable paresthesias around the mouth and at the finger tips the muscle twitchings and general nervousness although alleviated by calcium gluconate. *Disopropyl fluorophosphate* has been tried lately by Comroe and others because of its prostigmine like action. It is supposed to have a more prolonged but less efficient action than prostigmine and larger doses produce unpleasant reactions on the part of the nervous system. *Amino acid (amigen)* has been given by Torda and Wolff in combination with prostigmine and found effective. Its practical use in critical prostigmine resistant conditions has yet to be worked out.

Thymus Therapy Although the role played by the thymus gland in myasthenia gravis is obscure tumors of the thymus (15 per cent according to Good) as well as

thymic abnormalities have been found in such a high percentage of cases (50 per cent according to Gillespie) that there is no doubt that the function or dysfunction of the thymus affects sustained muscle contraction. Adams and Allan suppose that the mere presence of the thymus may be responsible for the myasthenia in sensitized individuals. Thymomas usually benign are found much less frequently than hyperplasias which resemble hyperplastic lymph

30 gm has been shown to have no relation to the severity of the disease (Keynes). Treatment with thymus extract has no specific effect.

Thymectomy has been done since 1908 when Suerbruch performed the first operation of this kind. Adams and Allan have recently computed the results of 129 operated cases and found that 17 patients recovered completely, 24 were considerably improved, 27 moderately improved, 2 slightly improved and the others were either not improved at all or had died. This would mean that 57 per cent were significantly benefited by thymectomy. Blalock and his co workers as well as Keynes call the results of the operative treatment encouraging.

It is certainly a responsible task. The risk is due partly to the difficulty of the operation itself especially in the presence of a tumor and partly to the character of the disease which with its threat to respiratory failure would make any major operation extremely hazardous. It is felt that patients with mild cases and patients beyond the age of 35 or 40 should not be operated on. The presence of respiratory difficulties is a contraindication to the operation but once these are overcome and a remission of several months has been established by prostigmine and rest therapy such difficulties may not exclude the patient from surgery. Every severe case of myasthenia in a young person should be treated with prostigmine in an optimal manner for several months before thymectomy is considered. Even then the possibility of spontaneous remission will raise doubts as

to the advisability of surgery. The degree of the patient's lasting disability will weigh the scale in favor of thymectomy.

As shown in the above figures the clinical results of the operation indicate that the majority of patients operated on still need medical care which means that cure is not established. Thymectomy for a thymoma verified by roentgen ray but without myasthenia gravis signs should be viewed with great reserve even though Murray and McDonald have stated that almost all patients with thymoma eventually develop myasthenia gravis.

Irradiation of the thymus whether the gland is visibly enlarged or not is still more difficult to evaluate as to success than thymectomy. Eaton states that of 100 cases only 18 showed a remission during the ensuing 12 months. But this statistical evidence may be misleading because as Eaton says cases too ill for an operation were included and the amount of roentgen irradiation given was often insufficient. Anna Hamann, the well known radiotherapist, gives her experience with irradiation of the thymus as follows:

In a small number of patients with myasthenia gravis encouraging results have been reported after roentgen and radium irradiation to the thymus gland.

Lymphosarcoma the most common malignant thymus tumor associated with myasthenia gravis is as a rule highly radiosensitive. The hyperplastic thymus is also radiosensitive while thymic carcinoma is radioresistant and myosarcoma is of moderate radiosensitivity.

If the malignant nature of a thymus tumor is verified intensive radiation with a total dose of 3000 r or more within the tumor is indicated. Though thymic enlargement caused by lymphosarcoma may completely disappear after a small dose of a few hundred r only the high total dosage is necessary for a lasting effect.

Thymus hypertrophy may regress after small doses in the order of 600 to 800 r tissue dose in the thymus. Therefore in patients with myasthenia gravis without demonstrable thymic enlargement or in cases with enlargement of unknown nature roentgen therapy with moderate dosage of about 800 r in the thymus is being given and eventually repeated depending on the clinical course. Two or three of such courses given at intervals of two to three months are safe.

Roentgen therapy is administered as fractionated irradiation with daily surface doses of 200

to 300 r. Two anterior chest portals are sufficient for moderate total dosage in the thymus while for high dosage in malignant tumors cross fire from additional posterior chest portals and supraclavicular portals is necessary.

In lesions of moderate radiosensitivity regression of thymic enlargement and improvement of the muscular symptoms may be observed after 2 or 3 months only. Improvement of muscular symptoms has been reported with and without demonstrable change in the thymus. Adequate irradiation does not interfere with later surgery.

While radiation therapy in the hands of an experienced radiologist is without risk it has to be known that highly radiosensitive tumors may react with increased potentially dangerous swelling to excessive daily irradiation doses.

There is evidence that in patients in whom thymectomy is contraindicated judicious irradiation by an experienced radiologist may be a worthwhile procedure.

Drug Contraindications First of the drugs to be avoided in myasthenia gravis is curare the effect of which on muscular contraction resembles the underlying pathology of myasthenia. Patients selected for curare treatment whether in combination with shock therapy or for muscular spasticity should first be tested for curare sensitivity. Bennett and Cash have shown that 1/6th to 1/4th of the average curare dose may precipitate muscular weakness even when given to non myasthenic patients and may cause possible respiratory difficulties in patients with a latent myasthenic condition. Thyroid medication increases myasthenic symptoms and signs and is of no help even in patients with a low basal metabolism. Eaton reports that although hyperthyroidism complicated 6 per cent of his myasthenic patients thyroidectomy and the use of thiouracil were not beneficial in the average case. Quinine is known to increase muscular weakness in myasthenia and therefore a myasthenic patient with malaria should be given atabrine or some related drug that has no effect on myasthenia.

FREDERICK HILLER

REFERENCES

- Adams R and Allan F N: Thymectomy in Treatment of Myasthenia Gravis. *Dis. of Chest* 13:436 1947.
 Allan F N: Myasthenia Gravis. *Lancet Clin. Bull.* 2:11 1940.
 Bennett A and Cash P T: Myasthenia Gravis.

- Curare Sensitivity, New Diagnostic Test and Approach to Causation *Arch Neurol & Psychiat*, 49 537, 1943
- Blalock, A et al Treatment of Myasthenia Gravis by Removal of Thymus Gland, Preliminary Report *JAMA*, 117 1529 1941
- Comroe, J H, et al Effect of Di-isopropyl fluorophosphate (DFP) upon Patients with Myasthenia Gravis *Am J M Sc*, 212 641, 1946
- Eaton, L M Care of the Patient Who Has Myasthenia Gravis *M Clin North America* 31 907, 1947
- Gillespie, H Thymoma in Myasthenia Gravis *Arch Path*, 32 659, 1941
- Good, C A Roentgenologic Findings in Myasthenia Gravis Associated with Thymic Tumor *Am J Roentgenol*, 57 305 1947
- Keynes, G, Collins D H, and Martin J P Symposium on Surgical Treatment of Myasthenia Gravis *Proc Roy Soc Med*, 39 600, 1946
- Murray, N A, and McDonald J R Tumors of Thymus in Myasthenia Gravis *Am J Clin Path*, 15 87, 1945
- Richter R Management of Myasthenia Gravis *M Clin North America*, 29 126, 1945
- Schwab, R S, and Viets H H Prostigmin Test in Myasthenia Gravis *New England J Med*, 219 226 1938
- Schweitzer, A Myasthenia Gravis, Humoral Transmission of Nerve Impulses, and Thymectomy *Exper Med & Surg*, 5 264, 1947
- Torda C, and Wolff, H G Effect of Ammo Acids on Function of Muscles of Patients with Myasthenia Gravis *Arch Int Med*, 80 68, 1947
- Viets, H R Myasthenia Gravis *JAMA*, 127 1089 1945
- Viets, H R, and Mitchell, H S Prostigmin Test in Myasthenia Gravis *New England J Med*, 215 1064, 1936
- Viets, H R, and Schwab, R B Prostigmin in Diagnosis of Myasthenia Gravis *New England J Med*, 213 1280, 1935

DISEASES DUE TO ALLERGY

ALLERGY OF THE NOSE AND NASAL SINUSES

Allergy of the nose and nasal sinuses can best be discussed as it occurs, seasonally and perennially

Allergy of the nose and nasal sinuses is a frequent condition, characterized by edema of the mucosa of the nose and nasal sinuses

mon in rhinitis due to fungi, house dust, animal danders, etc

Bronchial asthma probably follows in about 40 per cent, but proper care from the allergic point of view will usually prevent the onset of asthma

Many individuals have both seasonal and nonseasonal rhinitis. Some who think they have only hay fever will state on close questioning, that they have frequent "colds" which last a short time and are not infectious. Such individuals usually give positive skin tests to both pollen and non-pollen allergens, e.g., fungi, house dust or feathers. Nasal polyposis is uncommon in seasonal hay fever probably because the season is so short that the nasal mucosa cannot develop enough prolonged edema to force the formation of polyps. In perennial rhinitis, however, symptoms may be more or less constant with a much greater tendency to the formation of polyps. If the polyps become large they may press on certain "trigger" areas with resultant attacks of asthma.

In all types of allergy of the nose and nasal sinuses there is the fundamental allergic basis (see section on Bronchial Asthma). This is characterized by (1) a constitutional basis, usually by heredity, (2) contributory factors, such as mechanical dusts, chemical fumes, endocrine and psychogenic stimuli,

and such physical agents as heat or cold, and (3) exciting allergens, e.g., pollen, fungi, house dust, or foods.

In all of these groups, therefore, one usually finds eosinophilia in the blood and nasal secretion, a history of allergy in the family, or other allergy in the patient, and positive skin tests.

The nasal smear for eosinophilia is extremely important and credit goes to Hansel who has emphasized its diagnostic significance. The smear is best collected by having the patient empty his nasal secretion into a cellophane handkerchief. The material is then fixed and stained (Wright, Giemsa or Hansel stain). Eosinophils in nonallergic cases should not exceed 4 per cent of the cells present. In nasal allergy eosinophilia frequently reaches 50 or even 100 per cent—such high percentages are diagnostic of allergy. If a patient with nasal allergy develops an infectious "cold" (acute coryza), the nasal eosinophilia will decrease or disappear and the cells in the nasal secretion will be chiefly polynuclear neutrophils. After the acute "cold" is over, eosinophils will reappear and replace the neutrophils.

Hay Fever (Pollenosis) Hay fever is a seasonal condition caused only by pollen, characterized by inflammation of the nose, eyes, and throat, often complicated by bronchial asthma, sneezing rhinitis, and conjunctivitis, with itching, are usually present (Unger). It occurs in about 4 per cent of the population of the United States, probably less in other countries because of the absence of ragweed. Asthma accompanies or replaces the hay fever in about 40 per cent of cases, and sinusitis and chronic bronchitis may also occur. Polyposis is rare, and emphysema seldom occurs in uncomplicated pollen asthma because there is ample time for restoration to normal before the next season.

ETIOLOGY In general, in this country, the three hay fever seasons coincide with the

amount in the air of pollen of certain trees, grasses and weeds. These light, buoyant pollens may be carried for long distances by the wind. Pollen from flowers, on the other hand, are sticky and chiefly carried by insects, and hence are of only local importance as causes of hay fever. When the pollen count is high, symptoms are apt to be severe in those who are allergic to the particular pollen. When the pollen count is low, hay fever symptoms are usually mild or absent. Asthma can, however, occur in stormy weather when the pollen count is low.

In central and northern United States pollen from elm, maple, ash, oak, and other trees is in the air from about March to May or June. Pollen from June grass, timothy, red top, and orchard grass abounds from the end of May to about mid July. Giant and short ragweed pollen causes much suffering more than the other two combined, from about mid August to the end of September. These dates are only approximate and depend on the weather and the location.

Other important pollens come from Russian thistle, Kochia, wormwood (sage), hemp, pigweed, burweed, marsh elder, cocklebur, and lamb's quarter. Other sections of the country have other offending agents. Grass, especially Bermuda grass, is much more important in the south, also west of the Rocky Mountains. Some sections have two grass hay fever seasons. Mountain cedar pollen causes much hay fever around Dallas and San Antonio in December, January, and February. Ragweeds are practically nonexistent west of the Rockies and outside of this country are found only in southern Canada and northern Mexico, with a few minor exceptions.

For further details regarding pollen the reader is urged to consult Unger, Durham, and Vander Veer. Much information can also be obtained from those who manufacture pollen extracts.

TREATMENT Treatment can be divided into preventive, specific and symptomatic. All three are important.

Preventive Measures Children of allergic parents should be skin tested for pollens before they go to a camp where the pollen count may be high. If the test is positive, they must not go to that camp while the particular pollen is in the air. Once a pa-

tient's hay fever threshold (resistance) is overcome it may be difficult or impossible to restore it completely.

Allergic individuals should not move to areas, e.g., suburbs, where the pollen count may be higher. Several of my patients have moved to suburbs which have many oak trees, and being sensitive to oak pollen they have experienced increase of symptoms. Advise from a physician before moving may prevent suffering.

Destruction of weeds automatically lessens hay fever. To date there has been no concerted effort along this line, though such action is highly desirable. Pollen can travel more than 400 miles so that the problem is not too simple. Perhaps the use of chemicals will prove more effective than have weed pulling and cutting.

Filters are useful. These can be installed in windows and most of these machines filter out 95 to 99 per cent of the pollen. Nasal filters have been only mildly successful and most patients do not use them. Places which are air conditioned are practically pollen free and similarly, pollen is almost entirely absent in rooms with shut windows.

Avoidance of hay fever areas is of aid to those who can travel each hay fever season. Those who are allergic to ragweeds obtain almost complete relief west of the Rockies and in Florida. Those who are sensitive to mountain cedar need only travel about 200 miles. Those who are grass allergic may obtain relief above the timber line.

Proper hyposensitization with pollen extracts almost always prevents the onset of asthma in that particular season.

Specific Measures Specific measures have been used for many years, with considerable success, although complete elimination of symptoms is not usually obtained. *Hypo sensitization* usually prevents pollen asthma and usually lessens hay fever symptoms (approximately 75 to 85 per cent).

The pollen extracts must be carefully chosen, e.g., patients who are allergic to ragweeds must receive injections of ragweed extracts, not of grass.

Injections can be given preseasonally, seasonally, and perennially. Each method has its own function.

The preseasonal method is most widely used. The initial dose is usually 0.10 cc. of

the 1 10,000 dilution injected subcutaneously but if the local reaction is large the initial dilution should be 1 100,000 or even 1 1,000,000 Each succeeding dose should then be

small doses e.g., 1 10,000, most men do not give doses larger than 0.50 cc., 1 100 (The writer favors large doses, up to 6 per cent if the patient can tolerate such amounts His experience definitely shows that those who can take large amounts almost always obtain better results than those who develop reactions with smaller dosages)

Injections should begin as soon as the diagnosis is established The intervals of treatment should be adjusted so that the patient receives 25 to 40 injections if possible before the next hay fever season starts In the following schedule a typical pre-seasonal ragweed series is shown

SCHEDULE OF PRESEASONAL TREATMENT

Injection	Dilution	Dosage Injection (in cc)	Injection	Dilution	Dosage Injection (in cc)
1	1 100,000	0.10	17	1 1000	0.22
2		0.15	18		0.30
3		0.22	19		0.45
4		0.30	20		0.65
5		0.45	21		0.85
6		0.65	22	1 100	0.10
7		0.85	23		0.15
8	1 10,000	0.10	24		0.20
9		0.15	25		0.25
10		0.22	26		0.30
11		0.30	27		0.35
12		0.45	28		0.40
13		0.65	29	3 per cent	0.15
14		0.85	30		0.17
15	1 1000	0.10	31		0.19
16		0.15	32		0.21

In the above series, injections in the first two or three dilutions are usually given twice a week, the stronger injections once a week, then once in 2 weeks If there is plenty of time the injections may be started on a once a week schedule, instead of twice if rushed, the first injections should be given three times a week

During the hay fever season which follows this pre-seasonal treatment the dosages should be reduced about 25 per cent and given about once a week If severe hay fever is present the amounts should be still further reduced

After the hay fever season is over the perennial method begins Treatment is not

continued until the next pollen season again lowered approximately 25 per cent during the season, and again gradually increased after the pollen is no longer in the air There are fewer reactions and better results by this method than can be obtained by repeating year after year pre-seasonal therapy

Co seasonal treatment is advised for those

repeat this daily or every other day for three injections, then increase to 0.04 cc. for 1 or 2 injections then 0.06, 0.08, and 0.10 cc The results are sometimes surprisingly good The usual pre-seasonal dosages are given after the hay fever season is over, followed by perennial treatment

By these methods better results for each patient are usually obtained each year, then injections may be stopped in some cases Unfortunately, there are some depressing exceptions in which hay fever seems to occur year after year, despite what we deem sufficient and correct therapy

In pollen asthmatic patients treatment should not be stopped but should be continued at 2 to 4 week intervals year after year It has been our experience that such treatment usually prevents or markedly lessens asthma We have also found that asthma almost always returns the first season for which injections have not been given and such asthma is frequently so severe as to necessitate hospitalization

Excellent durable pollen extracts can be made with glycerin, and short lasting solutions with sodium chloride The best extracts, in the writer's opinion are those made with dextrose These extracts are clear, stay potent as long as those made with glycerin, and, above all do not sting or hurt on injection Our formula is

Dextrose, C P	45 gm
Phenol C P	5 gm.
Sodium bicarbonate, C P	2 gm
Distilled water to make 1000 cc	

Local and general reactions can occur if there is much local inflammation the preceding dosage is either repeated or reduced. This precaution usually prevents constitutional symptoms which would almost certainly occur if dosages were increased. But if asthma, hay fever, or urticaria should occur as a result of an injection, the patient should receive epinephrine 0.5 cc of 1:1000 dilution subcutaneously and/or aminophylline 250 mg intravenously, and his next dosage should be sharply reduced. All patients should sit in the doctor's office for at least 15 or 20 minutes after injections of these extracts and the site of injection should be inspected before the patient departs. A tourniquet should be used for 5 or 10 minutes above a severe local reaction. Itching of a hand after an injection is a definite warning that any further increase in dosage probably will bring on a constitutional reaction. With care our percentage of reactions has been markedly reduced.

Oral pollen therapy has been used by some but it has rightly fallen into disuse. The results are poor as compared to those obtained by injections, and severe gastro-intestinal symptoms have occurred.

The mechanism of hyposensitization is not too clear although considerable success is obtained in most cases. The role of the blocking or inhibiting antibody of Cooke is uncertain. This new antibody is found in patients who have received a series of injections of pollen extracts but it is also found in normal persons who have been given similar injections.

Failures from hyposensitization usually result from incorrect choice of pollen extracts, or to dosages which are too weak or too strong for that patient, or to the use of deteriorated extracts or to the failure to test for and to remove during the hay fever season extrapollen substances which aggravate symptoms.

Symptomatic Treatment Symptomatic treatment of hay fever is also important, especially since the recent introduction of the new antihistaminic drugs. Up to that time our symptomatic measures were not too effective. The large number of available medicines and methods demonstrated the uselessness of most of them.

Ephedrine, locally and by mouth gives

some relief. It makes patients "nervous" and should be combined with a sedative, e.g., secobarbital. The more one uses "nose drops" the less one is impressed, though there is no objection to the occasional use of a nasal vaporizer or of an ephedrine or similar jelly to relieve severe nasal blocking. Neosynephrin in 0.25 per cent solution is about as effective as ephedrine, and many pharmaceutical firms have other drugs of similar nature.

For many years our patients have been helped by the following prescription for the conjunctivitis of hay fever:

Epinephrine hydrochloride	mm xv
Dilute acetic acid	mm v
Resorcinol	gr m
Distilled water q s ad	℥ i

Fac solut. Sig. One drop in each eye as nec for hay fever.

Operative treatment for hay fever is usually unsuccessful, but, if indicated for infectious sinusitis or markedly deviated nasal septum, the procedure should not be carried out during the hay fever season. Nasal cauterization is now rarely done, and removal of tonsils and adenoids does not help hay fever, if indicated for other reasons it, too, should be performed outside of the pollen season.

The new antihistaminic drugs constitute a definite aid in the treatment of all kinds of allergic rhinitis. Benadryl (B dimethylamino ethyl benzhydrol ether) and pyribenzamine (pyridyl N' benzyl N dimethyl ethylene diamine) are the most widely used in this country. Other members of this group include antergan, neoantergan, antistin, theophorin, thenylene, neohetramine, histadyl, and others.

All of these drugs are supposed to neutralize the effects of histamine, and they all do this to a greater or lesser extent, both in experimental animals and in man. However, they have little effect in lessening the output of gastric juice brought on by an injection of histamine. Ratner, whose views are shared by many, concludes that the release of histamine has not yet been proved to be the fundamental factor in anaphylaxis or allergic reactions, hence any therapy based on such a concept must be called into question.

All of these "antihistaminic" drugs have now received considerable trial. Benadryl

and pyribenzamine have been most widely used, and the results in all types of allergic rhinitis have been about the same. This statement also applies to the other drugs of this group. All have successfully lessened itching of the eyes and nose and have decreased nasal blocking and rhinorrhea. They also lessen pruritus, and are useful in urticaria and angioneurotic edema. They are of much less help in bronchial asthma and in atopic dermatitis ("eczema").

All of these drugs have some disagreeable side effects, disagreeable but not dangerous.

The usual dosage in hay fever is about 50 mg every 4 or 6 hours, if and when symptoms occur. Some use these drugs prophylactically, others give them only when symptoms are present. Relief may last a few hours (Fenberg).

I agree entirely with Friedlaender and Friedlaender, who state "The antihistaminic drugs are purely palliative medication. They produce no lasting benefit and possess no curative effects. Chronic symptoms usually recur a short time after withdrawal of the drugs. . . Inasmuch as the effect of a single dose is of relatively short duration, they should only be employed where active symptoms warrant their use. The use of these drugs is not a substitute for the careful immunologic study necessary in each case of allergy. The determination of specific etiological factors, the elimination of the offending allergens where possible, or hyposensitization when necessary, are the sole means at present of achieving lasting results in allergic disease. The antihistaminics are valuable symptomatic drugs which may frequently afford the patient temporary relief from his discomfort until the effects of more specific therapeutic measures become evident."

The use of hapamine (histamine azopropylate) is also being employed. They are

many others are affected by inhalation of pollen, and others from both fungi and pollens. The important fungi are discussed in many references, especially by Fenberg and Unger. There are thousands of different kinds of fungi and our knowledge is still fragmentary, but enough is known about them to warrant the following statements:

(1) They abound in the air all year round, especially in warm weather. They are present, but in much fewer numbers, in winter.

(2) The total fungus counts are apt to be high in some places and low in others. According to Durham, for example, the total mold spore count in Phoenix, Ariz (1933) was only 160, and only 191 in New Orleans, whereas it was 17,280 in Springfield, Ill (1940), 17,131 in Moorhead, Minn (1937), and 16,139 in Dallas. Much territory needs to be surveyed, and we know that mold counts vary with the weather even more than do pollen counts.

(3) In some localities fungi cause more suffering than pollen. For example, in 1948 in Chicago we found on our exposed slides approximately 4,000 tree, 1,000 grass, and 5,000 ragweed pollens (total counts). By comparison, we counted over 20,000 molds and smuts, chiefly *Hormodendrum* and *Alternaria* molds. And, clinically, too, our impression was that suffering in 1948 came much more from fungi than from pollen. This was not true in other years, especially when there was a high ragweed count (up to about 13,000).

(4) The action of these inhalant molds and smuts (and yeasts to a much lesser extent) is like that of pollen—they act as allergens. They probably have no bacteria-like effect, as opposed to those fungi like *Actinomyces* which may be pathogenic. Since they act as allergens, they give almost as good positive scratch tests as do pollens, and are likewise positive in sensitive patients on testing by the intradermal, nasal, and conjunctival methods, also by passive transfer.

(5) The two most important molds in the central part of the United States are *Alternaria* and *Hormodendrum*. Durham concluded that "the largest *Alternaria* belt extended from the Rockies to the Appalachians, both coasts and the deep South being comparatively free." These molds are

recent years there has been a decidedly increased interest in the role of inhalant fungi, especially molds and smuts. Large numbers of patients develop rhinitis and/or asthma year after year from this type of allergy, just as

found chiefly from May to October, and are especially common in late July and early August, between our grass and ragweed seasons (Therefore if a patient has rhinitis or asthma at this particular time each year, he is apt to be allergic to Alternaria) Hormodendrum, on the other hand, is probably found all over the world and is less limited as to season. Other molds which may cause symptoms and which are used in extracts for hyposensitization are *Aspergillus*, *Penicillium*, *Helminthosporium*, *Mucor*, *Monilia*, *Phoma*, *Fusarium*, *Botrytis*, *Rhizopus*, *Chaetomium*, *Cephalothecium*, and occasionally others.

(6) The mold spore is the reproductive body and represents the allergenic part, extracts made from spores are usually potent and give good positive skin tests and can give local and systemic reactions in sensitive individuals. Extracts made from mycelia are of little value in testing or in treatment. Mold spores like pollen are light and small, and are wind borne and can be carried for long distances as shown by Durham, who reported the transportation, during a 1937 windstorm, of large numbers of spores from southern Minnesota to various parts of the eastern seaboard and to the Gulf of Mexico.

(7) Molds are counted by the exposed slide method as carried out for pollens. Mold colonies are also counted by culturing in Petri dishes. Not all molds can be identified by both methods.

(8) Smut grains can often be seen on exposed slides. Corn smut resembles a small ragweed pollen. They are especially common in showers in the summer and fall. They grow poorly in cultures. Corn smut is the most important, but smuts from wheat, rye, barley, oat, and Johnson grass may also cause symptoms, especially in farmers or in those who live close to farms, or in those who handle cereals (grain mill workers) (Witch). Smuts are probably the most allergenic factor in allergy from "farm dusts", these dusts are important causes of asthma and rhinitis. Mites and other insects, the cereals themselves and certain feeds may also harass the farmer. In our office we usually treat these patients, after positive skin tests to the mixed farm dusts and the individual components, by injections of a mixed farm dust extract.

(9) Yeasts often give positive skin tests, but more often in atopic dermatitis than in respiratory allergy. They are important enough to use in hyposensitization, as well as to avoid, as in bread, crackers, coffee cake, beer, and certain vitamins.

(10) Rusts from wheat are found on exposed slides. Cadham reported 3 cases of asthma supposedly due to inhalation of these rusts, but his findings have not been confirmed.

The diagnosis of inhalant fungus allergy is based on the usual history of seasonal symptoms which are increased with high fungus counts and lessened with low counts. In addition, skin tests are usually positive (scratch more reliable than intradermal), and other evidences of allergy are usually present.

In addition to atmospheric fungi, respiratory allergy may be caused by molds which grow in old bedding, in damp basements, on "moldy" articles, and on or in articles of food, e.g., tomatoes, bread, or cheese. Symptoms in such cases come at any time of the year—they are not seasonal.

Treatment of mold allergy is similar to that with pollen. Since mold seasons are longer it is more difficult to give injections preseasonally, but when possible this method beginning with about 1:10,000 or 1:100,000 is to be used, followed by seasonal and perennial treatment, as with pollen. If the patient reports during the season, dosages should be small and increased cautiously. Local and general reactions can occur, as with pollen.

The choice of the particular fungus extract is not always easy. It should depend on the correlation of symptoms with atmospheric counts and also, to a lesser extent, on skin test reactions to individual molds or smuts. Since *Alternaria* and *Hormodendrum* are probably responsible in 70 to 75 per cent of these cases they should make up the largest percentage of the extract. The other fungi are then added to make 100 per cent. If, however, there is strong clinical and skin test proof that the symptoms are due to *Aspergillus fumigatus* or to *Penicillium* or to corn smut, the particular allergen should be chosen, and the others may or may not be added. Some allergists routinely add about 10 per cent house dust extract to these

fungus extracts and add about 10 per cent in-
with
ood
as with pollen, i.e., about 75 to 85 per cent
of all patients receive more or less benefit
and in over 90 per cent a previous asthma
from fungi does not recur. The writer is par-
ticularly impressed with the brilliant results
usually obtained from injections of mixed
farm dust extracts (largely smuts) in farm-
ers and those who live close to farms. This is
in line with our findings that we almost al-
ways have good to excellent results if we
hyposensitize with an extract derived from
the premises in which the patients have
symptoms, e.g., dust derived from the
bakery, furrier, or upholsterer.

eg, Tucson and Phoenix, and perhaps this fact explains the good results which some patients have on moving to that region. Damp basements should be dried by calcium chloride sacks.

Avoidance of smuts may involve leaving a farm, but hyposensitization usually suffices.

The symptomatic treatment of nasal allergy due to fungi is similar in most respects to that of pollen hay fever. Conjunctivitis, however, is not nearly the problem with fungi that it is with pollen.

Allergic Rhinitis (Perennial, Vasomotor, Hyperesthetic) This is a common condition, already discussed to some extent. Its etiology and treatment are similar to those of bronchial asthma with which it is commonly associated. Few patients with asthma fail to have a preliminary or concomitant allergic rhinitis.

Allergic rhinitis, probably the best term, frequently is called sinusitis or just "sinus." At least 75 to 80 per cent of all so called "sinusitis" is due to allergy, as can be shown by the findings of allergy, heredity, nasal and blood eosinophilia, positive skin tests and relief from avoidance with or without hyposensitization.

pational dusts, cottonseed, and animal derivatives Allergy to foods can also cause allergic rhinitis

Infectious rhinitis should be easily differentiated from allergic rhinitis, especially by the absence of eosinophils in the nasal smear and the absence of other evidences of allergy (Hansel and Chang)

The treatment of allergic rhinitis is both specific and symptomatic. The specific measures are careful avoidance of the allergens, with or without hyposensitization, as with bronchial asthma. Good results are obtained in most cases, although much depends on the co-operation of the patient in removing or lessening exposure to house dust, etc.

The symptomatic treatment is similar to that outlined. Nose drops are used by some, ephedrine jelly temporarily opens blocked nostrils. The new antihistaminic drugs, e.g., pyribenzamine and benadryl, give good symptomatic relief in most cases but their use should never supplant specific allergy measures, including skin tests.

Surgical treatment is of little avail although marked polyposis should be taken care of, also severe nasal obstruction due to a deviated septum Sinus surgery should be reserved for infection only Cauterization and ionization now are rarely done Autogenous or stock vaccines are probably of some value, even when there is no definite evidence of infection Also, it is important to combat contributory factors, e.g., psychogenic, mechanical, estrogenic, or infectious

The results of treatment in allergic rhinitis are about on a par with those obtained in asthma. The most successful cases are those in which the exciting cause can be found and removed. The least successful are in that group in which the skin tests and nasal smears are negative, and especially in instances in which menstrual disorders seem to play a part. The administration of thyroid extract may help in those cases in which there is a lowered basal metabolic rate.

LEON UNGER

REFERENCES

cause, along with feathers, omis root, occu-

Cochran, R. A. Allergy to Penicillin and Its Treatment. *JAMA*, 111 24, 1938

Durham, O. C. Unusual Shower of Fungus Spores. *JAMA*, 111 24, 1938

Feinberg, S. M. Allergy to Fungi, in *Allergy in Practice* Ed. 2 Chicago The Year Book Publishers, 1946 Ch. 7, p. 224

Feinberg, S. M. Histamine and Antihistaminic Agents, Their Experimental and Therapeutic Status. *JAMA*, 132 702, 1946

Figley, K. D. Continuous Method of Hay Fever Treatment. *J Allergy*, 2 39, 1930

Friedlaender, S., and Friedlaender, A. S. Newer Antihistaminic Drugs in the Symptomatic Treatment of Allergic Manifestations. *Am Practitioner*, 2 643, 1948

Hansel, F. K. *Allergy of the Nose and Paranasal Sinuses* St. Louis C. V. Mosby Company, 1936

U. S. National Bureau of Standards. *Report on the Allergy of the Nose and Paranasal Sinuses*

Allergy in Etiology and Treatment of Nasal Mucous Polyps. *JAMA*, 103 1293, 1934

Phillips, E. W. Relief of Hay Fever by Intradermal Injections of Pollen Extract. *JAMA*, 86 182, 1926

Ratner, B. Evaluation of Benadryl Pyribenzamine and Other So-called Antihistaminic Drugs in Treatment of Allergy. *J. Pediat.*, 30 533, 1947

Unger, L. Other Allergic Diseases, in *Bronchial Asthma* Springfield, Illinois C. C. Thomas, 1945

Unger, L. Perennial vs Preseasonal Treatment of Hay Fever. *J Allergy*, 3 548, 1932

Unger, L. Preventive Treatment of Bronchial Asthma and Hay Fever. *Ann Int Med*, 4 1328, 1931

U. S. National Bureau of Standards. *Report on the Allergy of the Nose and Paranasal Sinuses*

Vander Veer, A. *Allergic Manifestations, Mechanism and Treatment* St. Louis C. V. Mosby Company, 1936

W. J. A. M. A., 91 200, 1931

Wittich, F. M. Further Observations on Allergy to Smuts. *Journal-Lancet*, 59 382, 1939

BRONCHIAL ASTHMA

Bronchial asthma is an allergic condition, occurring at any age, paroxysmal or chronic, characterized by wheezing, dyspnea, orthopnea, and cough, usually associated with rhinitis and with partial obstruction of the lower air passages.

Environment is important from the therapeutic point of view, especially as regards exposure to large amounts of house and oc-

cupation point of view, especially as regards exposure to large amounts of house and oc-

TABLE I

OCCUPATIONAL ASTHMA AND RHINITIS

Occupation	Chief Allergens
Aquarium supplies	Dermis root, water flea (fish foods)
Bakers	Wheat, corn, rye, buckwheat, spices
Barber (and beautician)	Orns, root, benna, dyes, karaya (Indian) gum, tragacanth, flaxseed, quince seed, hair, sheepwool, wool grease, oil of citrus group, essential oils
Bedding	(1) Feathers chicken, duck, goose, swan, pigeon, turkey (2) Animal hair horse, rabbit, goat, cow, hog, cat, sheep (3) Cottonseed, kapok, silk floss, flaxseed (4) Straw, corn husks, wood shavings
Brushes	Animal hair cow, hog, horse, goat, sheep
Butchers	Hair cow, sheep, hog, rabbit Insecticides, preservatives Borwood (sawdust) on floor Physical allergy (cold refrigerator)
Canners	Peas and beans infested with Indian meal moth
Clothing	Dyes Hair horse, goat, cattle, cat, dog, rabbit, camel, sheep wool
Eliminators	Pyrethrum, orns root, chemicals (DDT)
Farmer	Vegetables (tomato workers Cladosporium), cereals, etc. Livestock and cats, dogs, rabbits, etc. Poultry Cockroach Chicken coop mites, molds, smuts, feed (kamala) Pollen, molds, corn dust (smut) See Horticulturist
Florist	See Horticulturist
Flowers (artificial)	Feathers chicken, duck, goose, swan, turkey Silk Dyes
Flour Mill Workers	Grain smut and rust Wheat, rye, corn, buckwheat Molds, mites, pollen See Bedding
Furniture Furriers	Dyes Insecticides, sawdust (borwood), furs Fumes from cleaning fluids e.g. naphtha

TABLE I—(Continued)

Occupation	Chief Allergens
Gloves	Imitation furs cat, dog rabbit, goat, cow Hair rabbit, horse, sheep, goat, cat
Grain Elevator Operator	See Flour Mill Workers
Grocer	Coffee dust Flour dust Spices Boxwood (sawdust) on flour Fabrics cotton, wool, silk, furs Feathers duck, goose, ostrich chicken, pigeon Hairs horse, goat rabbit, sheep Bleaching agents banana oil, oxalic acid, dyes Flowers of all kinds Holland bulbs wormwood Hay, straw, grass mats, Pyrethrum Molds and fungi May and caddis flies other insects
Housewife	House dust feathers orns root pets Pyrethrum (insecticide), DDT
Insulators	Animal hair goat rabbit, hog Flax and straw Boxwood (sawdust) Cuttlefish bone Orange stick
Laboratory Worker	Hair guinea pig rabbit, dog cat horse mouse sheep
Metal Polishers	Rouge, resin bichromate, oxalic acid turpentine Linseed oil dyes, lead Acetylsal acid Arsphenamine Caroid Cocaine Codeine Dichloramine T Ipecac Lycopodium Methyl salicylate Peptone Podophyllin Poke root Pyrazinon Quinine Rhubarb Urease
Poultry	Feathers chicken, duck, goose, turkey Chicken feed linseed, castor bean soybean Mites smuts and rusts kamala powder
Printers	Acacia (offset spray), dyes glue
Rag Sorters	Wool, cotton silk, linen Dust Insects
Refrigeration	Sulfur dioxide

TABLE I—(Concluded)

Occupation	Chief Allergens
Rugs	Animal hair cat, rabbit cow, sheep, wool, camel, goat
Shoe	Lead Dyes See Glove
Tobaccoists	Tobacco (?) Perfumes Flavorings Cum tragacanth Cladosporium (mold)
Tomato Workers	Animal hair cat, rabbit cow, sheep goat, dog horse
Toys	Lead Dyes Glue Coffee Dust Cocoa Flour smuts and rusts molds Insects
Warehouse Workers	Animal hair goat horse sheep See also Barber
Wig Makers	

Three main etiologic factors are important in bronchial asthma, especially the third. These factors must be discussed because of their extreme importance as related to the treatment of the asthmatic patient.

(1) The constitutional basis is unknown, but heredity plays a large part, with a positive family history of one or more allergic conditions in at least 60 per cent of cases. The stronger this factor, the earlier is an allergic condition apt to develop in the children, a fact which we use to advantage in preventive treatment. In those whose asthma begins after 40, the hereditary factor is much less important.

(2) Contributory factors rarely, if ever, act as sole causes of asthma, but they may aggravate or incite attacks in allergic patients who are also exposed to the various exciting allergens listed in the next paragraph. These contributing influences may be mechanical, e.g., chalk and other dusts, chemical fumes of all kinds, various physical agents such as cold, heat, light or pressure, infections, especially the ordinary "colds", and psychogenic and endocrine stimuli. Since they aggravate symptoms they must be considered in treatment.

(3) Exciting substances (allergens) are the stimuli which bring on the attacks in sensitized persons. They usually act by inhalation, but can also act by ingestion or by injection. The chief allergens in bronchial

asthma and perennial (allergic) rhinitis are

(A) Inhalants

- (i) Pollen of trees, grasses, weeds
- (ii) Fungi mold spores, smuts, rusts, yeasts
- (iii) Animal hair, dander, feathers
- (iv) House dust
- (v) Cereals flour of wheat, corn, etc
- (vi) Seeds of cotton, kapok, flax, etc
- (vii) Miscellaneous orris root (cosmetics), Pyrethrum (insecticides), karaya gum (wax sets), certain powdered drugs, etc
- (viii) Occupational dusts, e.g., farmer, miller, furrier, baker, upholsterer, domestic

(B) Ingestants

- (i) Foods egg, wheat, milk, fish, pork, etc
- (ii) Drugs, especially aspirin

(C) Injectants

- (i) Overdose of extracts used in hyposensitization, especially pollen
- (ii) Drugs, e.g., morphine, arsphenamine, and vitamins
- (iii) Serums, e.g., tetanus and diphtheria antitoxin

(D) Miscellaneous mode of action not too clear

- (i) Bacteria and their products,—these important but not known whether primary or secondary in action
- (ii) Parasites e.g., Ascaris and taenia
- (iii) Silk
- (iv) Physical agents, e.g., cold or heat

Space will not permit further discussion. The etiologic factors are so important that the reader is urged to consult books and articles on this subject.

Cooke's postulates must be observed (1) the causative allergen must give a positive local reaction or must be able to cause the clinical symptoms, (2) the patient must have been exposed to this substance.

Pathogenesis As Related to Treatment.

Symptoms of asthma are almost always due to partial obstruction in the lower air pas-

sages. We now know that edema is the main factor, edema in the walls as well as in the lumina. Some of this watery fluid is exhaled and this often leaves behind thick tenacious sputum and pieces of mucus which obstruct breathing. In addition, there is often an increased secretion of mucus in asthma and in some cases spasm of the bronchial muscles may also occur. All of these factors tend to increase the difficulty and cause the lowered vital capacity always more or less present in bronchial asthma. In chronic asthma hypertrophy of bronchial muscles, as shown by Huber and Koessler, may still further lessen air space.

Histamine or a histamine like substance is thought by many to be elaborated during attacks of asthma by interaction of allergen and antibody in or at the sensitized bronchial cells. Despite many experiments this theory has not been proved, and there is much evidence against the hypothesis. The recently discovered "antihistaminic" drugs e.g., benadryl and pyribenzamine, have been almost totally ineffective in all but the mildest cases of bronchial asthma. Some of the recent literature on this subject has been discussed (Unger, Unger and Gordon).

Death in asthma is uncommon but it does occur, especially when morphine has been given in chronic asthma. This drug has no place in the treatment of bronchial asthma, as emphasized in Table II.

TABLE II

CAUSES OF DEATH IN BRONCHIAL ASTHMA

1 Asthma main or sole cause	21 cases*
2 Asthma a contributory factor	16 cases
3 Other causes (asthma not a factor)	11 cases

Cause of Attacks. Treatment in asthma and other allergic conditions gives best results when the cause of attacks can be found and can be partially or wholly removed. It is essential, therefore, to use every possible method and all clues to discover this cause.

Histories must be thorough and the patient must be permitted to talk without interruption. Removal of suspected factors

*Morphine known to have been injected prior to death in 6 of these patients.

may relieve symptoms, re exposure may bring on attacks. Correlation of symptoms with seasonal pollen and fungi counts is also important.

Skin tests should be thoroughly carried out, first by the scratch method. Intradermal tests should then be made if sufficient information has not been obtained. Skin tests only give clues, all positive reactions must be clinically correlated.

Therapy. Treatment is divided into preventive, specific, and symptomatic (non-specific) aspects. All are important.

PREVENTIVE. Preventive measures apply especially to children of allergic parents, since they are more apt to develop asthma and other allergic conditions than do children of nonallergic parents. The following points are important:

(1) These children should be shielded from the most common allergens, e.g., cats, dogs, feather or kapok pillows and comforters, fuzzy toys, andorris root (certain cosmetics). Damp basements may be full of molds. Pollens abound in vacant lots and at many day camps. Therefore these children should have tests for pollens before they go to camps. New foods should be added to the diet one at a time, a week apart, to see if symptoms result. Raw eggs should never be

raw foods. The home should be clean and no dusting permitted, a good vacuum cleaner, with attachments, is essential.

(2) Should mild allergic symptoms occur, a thorough allergy survey should be carried out at once. Children rarely "outgrow" asthma or other allergic conditions, it is easier to prevent chronic

asthma (the wheeze), hay fever, perennial allergic rhinitis, urticaria, and various types of gastro intestinal symptoms which, in these

cases, should also be undertaken, avoidance can not be complete.

(3) Allergic persons and their children should avoid "dusty" occupations (Table I), especially those of farmer, furrier, baker, upholsterer, domestic, and grain mill worker.

(4) We advise against intermarriage of allergic individuals but when love dictates, this advice is usually ignored. However if a healthy person inquires regarding a prospective marriage to an individual who has moderately severe or severe chronic bronchial asthma, I believe it is the duty of the physician to point out that further attacks are likely, that social and other activities may have to be curtailed, and that nocturnal symptoms are common, with resultant loss of sleep.

(5) Good nutrition and other hygienic measures are important especially as regards avoidance of persons with ordinary infectious "colds." Such "colds" are apt to bring on severe asthma, but only in allergic persons.

SPECIFIC TREATMENT. Our best results in asthma and other allergic conditions are obtained in those whose offending allergens have been discovered and can be removed. If such avoidance cannot be complete, hyposensitization is necessary, this is a measure which usually raises the patient's resistance so that he can withstand ordinary amounts of the causative factor. Many patients become symptom free, but permanent immunologic cure is rarely possible, as shown by recurrence of symptoms on re exposure to dogs, cats, or eggs, and by skin tests which usually remain positive even with no symptoms.

Elimination if complete, leads to relief from symptoms in paroxysmal asthma, although one cannot expect such an excellent result in patients who have chronic asthma with such complications as emphysema, atelectasis, or bronchiectasis.

tain wheat. Halfway measures often fail. Diet lists are essential, and at each office visit the patient is questioned as to possible exposures to a food allergen.

Those who are allergic to inhalant substances should also receive written instructions. Their homes should be as nearly allergen free as are most hospitals. No dogs or cats are permitted, even if skin tests to

these are negative Dust free covers or rubber bedding is advised in almost all cases Good vacuum cleaners with attachments are to be ordered, also *inoleum bottoms* to all soft furniture so that dust cannot fall to the floor Nonallergic cosmetics are advised The more thorough the elimination the better are the results

Hyposensitization (desensitization) consists of injections of increasing amounts of extracts of important allergens which cannot be avoided, e.g., pollens fungi, house and occupational dusts orris root animal danders, and cottonseed The oral method is occasionally used, but is not entirely successful

The technic is described in detail in Unger's *Bronchial Asthma* Briefly, injections are begun with weak dilute solutions and are increased approximately 50 per cent with each injection with due regard to local and general reactions The injections are usually given twice a week at first, later once a week, and then once in two weeks or even three or four weeks

The opening dilution is usually based on the size of the skin test to the particular allergen If the reaction to the scratch test is 4+ it is best to begin with 1 1,000,000 or even weaker If the reaction is smaller, one can usually start with 1 10,000 or 1 100,000 The final dilution varies with different allergists A few give only the weaker dilutions, but most men continue to increase to as strong an extract as the patient can tolerate

A typical dosage schedule is that which we use in hay fever (see section on Hay Fever) In that section, too, are remarks regarding frequency of injections and a consideration of local and general reactions

Injections in asthma are usually continued for at least a year, longer if symptoms persist From time to time the patient's condition is checked If he is not doing well several procedures must follow (1) Skin tests should be repeated, especially if asthma occurs during pollen or mold season or if a new clue is unearthed (2) The patient's home must be inspected to see if he is actually carrying out the instructions advised at the time of the first allergy survey, many patients are careless or unco-operative (3) A trial in an asthma room in a hospital is

often of great help in lessening symptoms (4) Some new type of therapy may be instituted, e.g., a new drug or a vaccine or other nonspecific measure

SYMPTOMATIC (NONSPECIFIC) TREATMENT
By the measures now to be discussed we seek to relieve the patient's symptoms We do not expect to prevent all further attacks of asthma, that is the function of the specific treatment just discussed

Symptomatic treatment can best be discussed as we see the patients, i.e., in their homes, in our offices, and at the hospital Certain measures are common to all

(1) Reassure the patient The attack of asthma may be the first or may be so severe as to frighten the patient and the family The physician should at once state that the attack will subside (and it almost always does) Death is rare in uncomplicated asthma unless morphine is injected Urbach was correct when he said "The asthma doctor must and dare not forget that his own quiet, deliberate and reassuring manner and his absolute conviction that almost all cases of asthma can be cured constitutes one of the most important prerequisites for success"

(2) Restrict the patient's activity in accordance with the degree of the asthma Some anoxia already exists, needless exertion only increases symptoms

(3) Aminophylline, given intravenously,

sure or pulse rate The drug is also useful when given rectally (10 grains in 20 cc tap water) or in 7½ grain (0.50 gm) suppositories By mouth it is of little use, and because of painful local reactions we do not inject the drug intramuscularly

(4) Epinephrine can be given in doses of 0.50 cc of the 1 1000 solution, intramuscularly in oil (1 500), and/or by inhalation (1 100) This drug also gives excellent results in most cases of asthma and is preferred in children It should not be used in patients who have already had too much epinephrine (epinephrine fast), as shown by pallor, tachycardia, and tremor It may be used in hypertension, but with caution and in small amounts

(5) Ephedrine in doses of ¼ to ½ gram (0.25 to 0.32 gm), orally, is useful in mild

and moderate asthma. Its effects are like those of epinephrine, with similar precautions. It is usually combined with a sedative, e. g., ephedrine or secobarbital.

(6) *Morphine should never be used in bronchial asthma*, it is too dangerous. It slows respiration and lessens the cough reflex and the expulsion of sputum thereby increasing anoxia. Its use frequently precedes a fatal attack.

Treatment of asthmatic patients in the home must be prompt and correct. The following measures are recommended:

(1) Reassure the patient (see above).
 (2) For adults give 10 cc aminophylline (8% grain or 0.24 gm) intravenously at once. The patient's arm should be horizontal and a good light is essential and the injection should take about 4 to 5 minutes. A 25 gauge 1 or 1½ inch needle is advised with a 10 cc all glass eccentric syringe. Nausea and vomiting will usually occur if the injection is given too rapidly.

(3) Then inject 10 cc of the 1:500 epinephrine in oil in the outer upper quadrant of the buttock, with precautions as with all oily preparations.

These two measures will usually break up an attack or give some measure of relief. Larger doses of aminophylline are not recommended. The injections may be repeated in 8 to 12 hours, if necessary. (The author urges all physicians who make house calls to pack in their bags the following: two or three 10 cc glass syringes with long thin needles, two or three 2 cc glass syringes, with wider needles, two or three 1 cc syringes and hypodermic needles, several 10 cc ampules each of aminophylline and 10 cc ampules of epinephrine in oil and a 30 cc bottle of 1:1000 epinephrine solution. The syringes and needles should be individually wrapped in paper and dry-sterilized (autoclave or oven). They are then quickly available when the patient is short of breath and the physician is short of sleep.)

After the patient has been more or less relieved the physician should check the home for possible clues to attacks, e. g., a dog or cat, kapok or feather pillows or comforters, horsehair mattresses, excess house dust, etc. At that time he should urge prompt skin tests and other detective measures, if not already carried out. The physician

should not be content merely to check attacks because if he does that alone the patient will often learn to treat himself and is much more likely to become a chronic sufferer than if examined from the allergy point of view. If the physician is not equipped for this allergy survey he should refer the patient to an allergist and the allergist should make the tests and send the patient back with the necessary suggestions for treatment. By this combination the patient will usually receive the best possible therapy.

A subcutaneous injection of 1:1000 epinephrine (0.20 to 0.40 cc) should be given to children followed by about 0.50 cc of 1:500 epinephrine in oil. In addition, we recommend syrup of ipecac, 1 teaspoonful every hour until vomiting occurs because expectoration of sputum usually accompanies emesis. It is in these children, especially, that prompt allergy surveys usually give excellent results.

Treatment in the office does not differ materially from that in the home. For severe attacks we give 0.24 gm aminophylline intravenously (slowly), followed by 0.50 to 1.0 cc epinephrine in oil (buttock). We also

tum, apomorphine is an excellent expectorant.)

Apomorphine hydrochloride	2 grains
Potassium iodide	5 drams
Syrup cherry q s ad	4 ounces
Sig	1 teaspoonful four times daily

At the office too the examination, fluoroscopy and laboratory and skin tests are carried out and these procedures are followed by the necessary injections of various extracts, e. g., ragweed or house dust, plus dietary and other instructions.

Treatment in the hospital is necessary for those patients who do not clear up at home and for those who have complications. The reader is urged to prepare in his own hospital at least two or three rooms for this purpose. Wesley Memorial Hospital (Chicago) has 12 beds especially designed for severe asthmatic patients. Filters in the windows over radiators clean the air and warm it in cold weather. The bedding is sponge rubber

or fiber glass. The floor is covered with linoleum. Each room contains 2 steel chairs with large dust proof leather cushions. Thin curtains are replaced every 2 weeks. Flowers, smoking and dusting are forbidden in these rooms; only wet mops are used.

Almost every patient whose asthma is due to inhalation of an allergen is quickly relieved in one of these rooms. If his symptoms are still present after 4 to 7 days he is probably allergic to a food or has some bacterial or other complication. Such rooms are therefore invaluable not only for treatment but also for causative differential diagnosis. An asthmatic patient commonly enters the hospital with severe asthma. After a few days in one of these asthma rooms he goes home asthma free. After a few days at home his asthma recurs and is relieved when he re-enters the hospital. Something in his home is the offending agent: usually house dust, a pillow or an animal. It is therefore important to clean up the patient's home from the allergic point of view while the patient is in the hospital. This procedure usually gives excellent results provided the home is made almost as dust free as is the average hospital. Bare floors or linoleum covered are

Oxygen inhalation is indicated in cyanosis or great weakness. It is of little use in simple asthma. Helium may be added but is seldom used.

Glucose is indispensable in asthma; it may even have a specific effect. Epinephrine forces glycogen from the liver and the glucose is doubly necessary for patients who have received much epinephrine. We give glucose intravenously and each patient also receives 5 oz. daily of glucose in the form of Dyno (Ratner) dissolved in a quart of fruit juices. This mixture is nourishing too; an important consideration in many of our asthmatic patients.

An instillation enema of 2 oz. of ether and 4 oz. of mineral oil may relieve severe spasms of asthma. A full ether anesthesia (30 to 40 minutes) may favorably terminate severe asthma (Unger).

The diet should be ample. If the patient cannot eat much because of dyspnea he should be encouraged to take frequent small meals.

Chemotherapy is not indicated in simple asthma but is if infection complicates the picture as shown by leukocytosis, crepitant rales, increased sedimentation rate and/or fever with or without abnormal findings in

While in the hospital the patient also receives therapy similar to that given at home. Aminophylline, however, is usually mixed with glucose by intravenous drip. For the first three days we usually inject once a day 0.48 gm. of aminophylline in 1 liter of 5 per cent glucose in water at 60 drops per minute. This procedure plus 10 cc. epinephrine in oil twice a day intramuscularly plus iodides and apomorphine usually relieve attacks.

If however asthma persists other measures become necessary. "Continuous" aminophylline by intravenous drip is usually successful (Goodall and Unger). The needle is left in the vein and 10 to 15 gms. of aminophylline are instilled with 1 liter of 5 per cent glucose at 28 drops per minute (2 liters in 24 hours). This drip may be continued for as long as a week or more if necessary and the amount of aminophylline in each liter is gradually reduced as symptoms subside.

without oxygen. Streptomycin has not been of much value in asthma.

The nose and sinuses should be examined in all asthmatic patients. Large polyps should be removed and severely deviated nasal septa should be straightened to prevent asthma from pressure on "trigger" areas in the nose. But the writer is opposed to operations on the sinuses unless there is definite infection as shown by pain, fever, leukocytosis and a nasal secretion which is high in polymorphonuclear leukocytes and low in eosinophils. The era of radical and almost indiscriminate nasal and sinus surgery has ended fortunately for patients.

Bronchoscopic aspirations may be lifesaving especially in patients who are unable to expectorate their thick, tenacious sputum. Suffocation may ensue if aspiration is too long delayed. The procedure in the hands

of an expert is indicated in all such patients no matter how near death may seem Morphine of course should not be used during the procedure

Sedation in asthmatic patients should be mild e.g. $\frac{1}{2}$ grain (30 mg) phenobarbital or $\frac{1}{4}$ grains (0.1 gm) of seconal

It is also necessary to treat all contributory factors as discussed in a preceding page The patient should avoid inhalation of various kinds of dust fumes bacteria and viruses and especially the common "cold" Psychogenic stimuli frequently aggravate asthma and may be checked by suggestion or other means It is more difficult to overcome endocrine influences e.g. that of oncoming menstruation Wet feet should be avoided also exposure to house cleaning especially

decorating are frequent causes of asthma They may be treated by applying heat to the chest or spleen and various types of fever treatment e.g. from intravenous typhoid vaccine or by diathermy may also be of aid in some cases Such agents probably act on some focal infection which should be removed

The treatment of complications of asthma will vary with the condition One must care for the asthma and at the same time attack the associated condition Lobectomy is indicated in asthma with bronchiectasis provided the patient is in good surgical risk and the dilatations have not involved too much lung tissue If an asthmatic patient needs an operation e.g. herniotomy or cholecystectomy he should first be made asthma free in the hospital (best in an "asthma" room) The operation is then performed and the patient returned to the "asthma" room to prevent recurrence of asthma which might interfere with the operation

22 asthmatic patients as compared to 6.4 per cent in nonasthmatic persons This percentage of recurrence would be greatly decreased if the patient were kept in an asthma room until the surgical scar is fairly strong

Results of Treatment in Bronchial Asthma Results in paroxysmal asthma are usually brilliant if the above procedures are carried out especially in patients who have had a careful history examination and complete skin tests and laboratory studies All this must be followed by avoidance of offending allergens with hyposensitization when these allergens cannot be completely avoided by the patient

Symptoms in chronic asthma can usually be lessened but complete relief cannot be expected because of such irreversible changes as found in the associated emphysema

The results are therefore best in children who usually have the paroxysmal type of asthma as shown in Tables III and IV

TABLE III
RESULTS OF TREATMENT IN 459 CASES OF
BRONCHIAL ASTHMA

Age at Onset	PAROXYSMAL					CHRONIC			
	100 per cent Cured	Imp. cond.	L. n. m. p. cond.	D. ad.		100 per cent Cured	Imp. cond.	L. n. m. p. cond.	Dead
0-9	55	81	5	3		—	12	9	5
10-19	9	29	0	1		2	13	9	4
20-29	17	27	4	2		—	8	10	4
30-39	8	17	5	1		—	11	7	—
40-49	4	17	—	3		2	7	9	11
50-59		2	1	2		—	9	4	4
60-69		—	—	—		—	1	—	3
Totals	93	173	21	11		4	72	49	37

* In a recent paper Harvey has presented evidence that the adrenocorticotrophic hormone (ACTH) is of value in treating patients with severe intractable asthma The administration of the hormone for 4 to 5 days in a dosage of from 100 to 500 mg daily produced an immediate remission lasting for an indefinite period in some patients In the patients reported cortisone was found not to be nearly so effective as the adrenocorticotrophic hormone Editor

Harvey A. McG. The Effects of ACTH and Cortisone in Allergic Diseases (To be published read before the American College of Physicians Boston April 1950)

has been shown through five generations by Osler Fairbanks and Crowder and Crowder Migraine and urticaria not infrequently co exist

The cause of attacks is varied In the acute cases certain foods and certain drugs are almost always the exciting factors and it is usually not difficult to track these down and avoid them The foods which are likely to cause these swellings are fresh fruits e.g. peaches and strawberries fresh vegetables e.g. tomatoes pork products (any variety) nuts shellfish and perhaps eggs and chocolate Milk in a few cases is undoubtedly a cause and milk from one herd of cows may incite hives while that from cows in other parts of the country may not be troublesome It may well be that the antigenic effect of milk depends on the type of food or grazing given the cows It has also been shown that patients are not necessarily sensitive to berries or other fruits but rather to something on the outside of these fruits Benson has shown that hives will not occur even in a strawberry sensitive individual if the berries are thoroughly washed in a colander under hot running water Such facts may account for the poor results with skin tests in this type of allergy As a matter of fact the information obtained by skin tests in urticaria and angioneurotic edema is almost always unreliable This writer has therefore discontinued skin testing in this group unless the patient has some other allergic condition Passive transfer tests at this time are useless

Drugs are more likely to lead to angioneurotic edema than are foods especially such drugs as quinine aspirin arsphenamine

less severe urticaria and occasionally angioneurotic edema The rash resembles that of serum sickness in that it often begins from 5 to 10 days after the drug has been used the rash may also begin quickly The lesions may follow injections of these antibiotics or may occur when the drugs are ingested or even after inhalation When a drug is applied as in an ointment any resulting lesion is usually that of a dermatitis at the site of application (contact dermatitis) rather than a generalized urticaria Occasionally however a widespread exfoliative dermatitis may oc-

cur but this is not usually of an urticarial type

Acute urticaria can also promptly follow an overdosage in hyposensitization (as in the treatment of asthma or hay fever) It can also occur and be troublesome in patients who need and receive insulin liver extract or other endocrine products The role of inhalation has not been proved it has been difficult to show that inhalation of house dust can cause hives Inhalation of silk can Acute hives can also occur from such physical agents as cold heat or pressure But in such cases the hives are not as red and itching is frequently absent The lesions themselves are sharply outlined and in this physical allergy type there is no pseudopodia as occurs in ordinary hives Infection is probably not important in acute hives except as it may lead to the use of a drug

Chronic urticaria and angioneurotic edema are markedly different from the acute types because the condition tends to drag on and to puzzle both the patient and the physician The food factor is certainly less important unless the antigenic food is one which is commonly eaten e.g. milk Drugs too are less frequent offenders though one must search for such substances as phenobarbital cathartics and ingredients in tooth pastes and mouthwashes In addition coal tar products are commonly used in certain prepared foods e.g. the substitution of vanillin for vanilla

It is in this group that infections seem most important especially those in the biliary tract as well as in the teeth tonsils sinuses prostate and pelvic organs Every sufferer with chronic hives should be searched for all these possible foci of infection It is especially important to do a roentgen ray of the gallbladder by the Graham Cole technic We have been able to clear up obstinate cases by finding and removing gallstones in patients who denied biliary tract symptoms

Other predisposing factors may also be of some importance e.g. endocrine and psychoneurotic and efforts along this line may be necessary Urticaria factitia (straight raised red lines due to scratching) is not really urticaria

Treatment ACUTE URTICARIA AND ANGIO-NEUROTIC EDEMA It is necessary first to give

relief and to avoid substances e.g. more antibiotics which might aggravate the condition. Two types of therapy are available: the new antihistaminic drugs and epinephrine or ephedrine. Almost all of the drugs of the first group give good results in these acute cases. After trial and error in many cases we have now systematized the treatment as follows. In severe cases we try to hospitalize the patients and give (adults) 100 mg. of pyribenzamine three times a day with 100 mg. of benadryl at night. In some cases we also inject about 0.50 cc. 1:1000 epinephrine as necessary and may also inject 10 cc. epinephrine in oil intramuscularly twice a day. Antihistaminic drugs can also be inserted under the skin. In milder cases 50 mg. dosages of an antihistaminic drug may suffice and epinephrine or ephedrine are usually not necessary.

It is also advisable to order a saline cathartic to remove as much as possible of the offending food or drug. Local applications may be soothing e.g. calamine lotion or baking soda or cornstarch baths.

Avoidance of the cause is of course of fundamental importance. Sometimes the cause is obvious e.g. the condition may follow injections of penicillin or ingestion of a drug such as quinine or of such a food as lobster or berries. But when the antigen is not evident we advise elimination diets. The patient is kept away from all medicines and cathartics (except those we give) and from the following foods: fresh fruits and vegetables and their juices (frozen foods are considered fresh); peas, beans, tomatoes in all forms; fish and nuts of all kinds; pork including ham, bacon, lard and some gelatinous compounds; chocolate and cocoa, chicle (chewing gum) and cola drinks. This diet is successful in many cases. If the hives disappear the diet should be maintained for about 2 weeks, then one food at a time is added with 4 or 5 days between additions to see if symptoms return. If milk is suspected the patient may be put on a strict milk-free diet or may be given only milk and cream to see if the urticaria is aggravated. Hyposensitization is rarely advised.

CHRONIC URTICARIA. In this condition the elimination diets and withdrawal of all drugs should also be tried, but the results are less successful. Infection is important in these

chronic sufferers and every effort should be made to discover and to remove any focus of infection especially in the gallbladder. Any measure which can allay psychic or endocrine factors may be useful, but too much reliance should not be placed on these factors. It is doubtful if true urticaria is due solely to a psychic or endocrine maladjustment.

Nonspecific measures are numerous and disappointing. Pancreatic extracts, calcium, autohemotherapy, ultraviolet light and injections of sodium thiosulfate, spleen extracts, peptone and vaccines have all been tried with indifferent results. Histamine and histaminase (torantil) are given by some workers. Dilute hydrochloric acid (30 to 60 minims) with each meal should help those whose gastric acidity is subnormal. High protein, low sodium acid ash diets have been successful in 6 cases of Rusk and Kenamore. Potassium chloride was substituted in place of sodium chloride. But Vaughan tried this regimen without success.

It is highly important that the physician should not give up hope in these cases. He should force his patient and himself to continue the search for possible clues. Sooner or later the cause can frequently be found. It must be admitted, however, that the lesions may spontaneously disappear, to the satisfaction of the patient and the bewilderment of the physician.

LEON UNGER

REFERENCES

- Benson R. L. Personal communication.
Crowder J. H. and Crowder T. R. Five Generations of Angioneurotic Edema. *Arch. Int. Med.* 20:840, 1917.
Fairbanks A. W. Hereditary Edema. *Am. J. Med. Sc.* 127:877, 1904.
Osler W. Hereditary Angioneurotic Oedema. *Am. J. Med. Sc.* 95:362, 1888.
Rusk H. A. and Kenamore H. D. Urticaria—New Therapeutic Approach. *Ann. Int. Med.* 11:183, 1938.
Unger L. Drug Idiosyncrasy. *J. Allergy* 3:76, 1931.
Vaughan W. T. *Practice of Allergy*. St. Louis, C. V. Mosby Company, 1939.

SERUM SICKNESS

Serum sickness (serum disease or serum

to the serum, not the antitoxin, and may be of the usual delayed type or it may be accelerated or atopic.

These reactions have been frequent since the introduction of diphtheria antitoxin in 1890 as especially noted by von Pirquet and Schick in 1905. In recent years reactions have probably been more frequent after tetanus antitoxin than with diphtheria antitoxin. With recent refinements in manufacture, delayed reactions are now decidedly less frequent.

The three types of serum reactions are as follows:

(1) The Usual Delayed Type. Fever, urticaria, adenitis, and joint pains frequently occur after the first injection of serum. Symptoms begin from the 5th to the 11th

especially if given intravenously. Age and sex apparently play no part. Although horse serum is the usual cause, hog and rabbit serum may also cause reactions and reactions occurred in the 17th century after transfusions of lamb's blood. Hives may be large or small and profuse or slight. The swellings of angioneurotic edema (lips, eyelids, various other parts of the body) may also occur, and the eruption may also resemble that of measles or scarlet fever, and may come in crops. Complications occasionally occur, e.g., neuritis, gastro-intestinal hemorrhage, abdominal pains, purpura, jaundice, hematuria, atrophy of the liver, Menière's syndrome, and psychosis. Leukopenia and relative lymphocytosis are frequent, but the blood findings are not diagnostic.

(2) Accelerated reactions are apt to occur in persons who have previously received serum, especially in those who have already had one or more bouts of serum sickness. The reactions come on much more quickly, often in a day or two, and occasionally immediately after the injection of the serum. The prompt reactions resemble those of anaphylactic shock in the guinea pig, and death may occur. Some of these patients have been sensitized by previous injections of serum and others by the now abandoned administration of diphtheria toxin antitoxin (now replaced by the use of diphtheria tox-

oid). This toxin antitoxin has sensitized from 25 to 27.9 per cent of children.

(3) Atopic reactions fortunately are rare as they are apt to be severe and often fatal. When antitoxin containing horse serum is injected into a person who is naturally allergic to horse dander, and who has bronchial asthma and/or allergic rhinitis, violent and immediate symptoms of anaphylactic shock may occur. The blood pressure falls, the white cell count goes down, and acute emphysema and pulmonary edema may follow. If death does not occur, asthma, urticaria, rhinitis, and/or angioneurotic edema may be present.

It has been shown that there exists an antigenic crossed relationship between sensitivity to horse serum and horse dander. Horse dander contains two antigens, the dander antigen and a small amount of the serum antigen. An individual allergic to both is apt to have reactions from injections of serum; but reactions are unlikely if he is only sensitive to dander. In other words, not all horse sensitive patients necessarily develop serum sickness if injected with horse serum. But the percentage is so high and the danger is so great in such persons that every precaution in giving antitoxin is essential, and some physicians simply refuse to use antitoxin in these horse sensitive individuals. It is in this group, especially, that the prophylactic use of toxoids is imperative, both diphtheria and tetanus toxoids should be given at once to these persons.

The treatment of serum sickness is that of prevention and that of the condition after it has occurred. The greatest advance lies in the field of prophylaxis.

Prevention (Prophylaxis). This involves (1) improvement in serum, (2) care in injecting antitoxin, (3) the use of antitoxins made from other animals, (4) the use of desensitized antitoxins, (5) the simultaneous use of epinephrine and/or antihistaminic drugs, (6) the role of anesthesia, and, above all, (7) the use of toxoids.

(1) Purification and concentration of immune sera have reduced the severity and occurrence of the smaller (delayed) type of serum sickness. Whereas about 90 per cent of persons developed urticaria or other symptoms when antitoxin was first introduced, the percentage of reactions has now

THE ROLE OF ADRENOCORTICOTROPIC HORMONE (ACTH) AND 17-HYDROXY-11-DEHYDROCORTICOSTERONE (CORTISONE) IN PRESENT-DAY THERAPY

Whatever is here written will probably in large measure be outmoded within a short period after publication of this volume. In view of the widespread publicity, regarding the effects of ACTH and cortisone in a variety of disease conditions, it is pertinent

out that neither ACTH nor cortisone represents therapeutic agents. Rather, they must be considered to be investigative tools, by means of which disease processes may be studied. A consideration of the diverse group of diseases, which apparently can be altered by the administration of ACTH or cortisone suggests that the major changes are those induced in the host's response to his disease rather than in the disease process per se.

The use of adrenal cortical extract therapeutically is not new. Aqueous adrenal cortical extracts and the more potent lipo adrenal cortical extracts have been used as supportive agents for many years, particularly in the treatment of prolonged illnesses, severe infectious diseases, and diseases in which alterations of fluid and electrolytes have been of paramount importance. Until rather recently the importance of supportive adrenal cortex therapy has been underestimated and not well understood. Following early experimental results it was necessary to break down the general action of the adrenal cortex into three groups: (1) the electrolyte fluid regulating action, (2) the metabolic regulating action ("S" hormone), and (3) the androgenic action ("N" hormone). Compound A was first studied in the treatment of Addison's disease. It was noted that the hy-

poglycemic attacks, which so frequently accompany adequate control with desoxycorticosterone acetate (DCA) were absent when compound A was given with DCA. Compounds A and E were later found to have slight effect on the electrolyte abnormalities of Addison's disease when administered alone. More recent studies have shown that compounds E and F (11, 17 oxysteroids) are primarily effective in the metabolic regulating action of the adrenal cortex and only mildly effective in the other adrenocortical functions. It became apparent then that compound III would have only a secondary role in the treatment of Addison's disease, but might be a necessary factor in the adequate treatment of total and certain types of mixed adrenal cortical insufficiency. Further work suggests that there is some antagonistic action between the "S" hormones and DCA as some of the excessive sodium retention due to DCA overdosage may be relieved by the administration of compound E or F.

Adrenocorticotrophic hormone (ACTH) has also been used experimentally for many years. As its name implies, ACTH stimulates the entire adrenal cortex, thereby producing all three general adrenal cortical actions. It appears to have little if any therapeutic effect on patients with Addison's disease, supporting its role further as a purely adrenal cortical stimulator. Until recently, the chief clinical use of ACTH was as a test for the presence of adrenal cortical deficiency. The "alarm reaction" of Selye. Many investigators feel that both ACTH and cortisone may

be significant factors in both the "alarm reaction" and in the course of the "adaptation diseases" so well described by Selye.

At the present time, ACTH and cortisone have been used therapeutically in only a few disease entities, in most of which alterations in mesenchymal tissue seems to be a prominent feature. Hench et al. have produced rather striking remissions in rheumatoid arthritis, rheumatic fever, and disseminated lupus erythematosus. Thorne et al. have had equally good results with ACTH and cortisone in the same diseases and have added gouty arthritis to the growing list. Soffer et al. claim a remission in one case of myasthenia gravis following ACTH administration. The effects of both cortisone and ACTH in such varied conditions as agranulocytosis, essential hypertension, acute infectious diseases, nephrosclerosis, anaphylactoid reactions, ulcerative colitis, and certain mental diseases are under observation at the present time. Few conclusions may be drawn, however, it is fair to state that both drugs show promise as investigative and therapeutic agents and have produced marked remissions in the few conditions which have been studied and adequately controlled.

The recommended dosage for cortisone seems to range initially from 300 mg. of the acetate (Merck) to as little as 50 mg. daily as a maintenance dose. It is usually given intramuscularly in divided doses twice a day. ACTH (Armour's standard) has been given in doses ranging from 20 mg. to 100 mg. daily, divided into four doses. The maximal effective action seems to be from 8 to 12 hours after administration. The optimal dose must be established individually for each patient under treatment. Both drugs produce certain abnormalities when adequate amounts are given, thereby aiding the investigator in determining when the optimal therapeutic level has been reached. These changes include a marked drop in circulating eosinophils, a rise in the circulating neutrophils, a decrease in circulating lymphocytes, a rise in the uric acid creatinine ratio in the urine, a rise in circulating and urinary 11-oxysteroids, and an increased insulin tolerance. These drugs may also produce increased nitrogen excretion in the urine and hyperglycemia. ACTH in addition produces

an increase in urinary excretion of 17-ketosteroids, initial sodium and chloride retention as evidenced by urinary excretion of these ions, and initially increased potassium excretion. Clinically, a Cushing's syndrome and hyperglycemia may become evident. ACTH may also produce a transient hypertension, epigastric distress, a sense of exhaustion, and euphoria. It has been suggested that some of the side effects of ACTH may actually be due to small amounts of pressor substances from the posterior pituitary present as a contaminant as a result of the manufacturing process.

There has been much discussion regarding the dangers of ACTH and cortisone administration. It is certainly too early to draw conclusions regarding this matter, but at the present time most investigators think that the bad effects are transitory in nature. Thorne et al. feel that before treatment with cortisone is discontinued, the patient should receive simultaneous decreasing doses of ACTH to offset the decreased endogenous production of the corticosteroids. Both ACTH and cortisone may decrease the endogenous production of ACTH, and it seems wise to give these patients decreasing doses of ACTH during the withdrawal period.

In summary, let us reiterate that cortisone and ACTH promise to be of great value in the study of certain disease entities. Both drugs act primarily as adrenal corticosteroids. ACTH by stimulating release of adrenal corticosteroids, and cortisone by its action as one of the adrenal corticosteroids. Both apparently have the ability to alter the host's reaction to certain disease processes. Recent investigation with these drugs has stimulated great interest in the further study of the adaptation diseases described by Selye. Therapeutically they are of only minor significance at this time owing to the limited production of the drugs and the paucity of knowledge regarding their possible deleterious actions.

In the following references, the authors have attempted to list only those papers which have direct bearing on the therapeutic uses of ACTH and cortisone and to articles which are essential to the basic understanding of their mode of action.

RALPH E. DOLKART
STEPHEN L. ALDRICH

REFERENCES

- Albright F. Cushing's Syndrome. *Harvey Lectures* 33:123, 1943.
- Forsham P. H. et al. Clinical Studies with Pituitary Adrenocorticotropin. *J Clin Endocrinol* 8:15, 1948.
- Franks A. W. T. *Endocrinology*. 2nd ed. New York: Macmillan, 1949.
- Hench P. S. et al. Effect of a Hormone of Adrenal Cortex (17 hydroxy 11 dehydrocorticosterone Compound E) and of Pituitary Adrenocorticotrophic Hormone on Rheumatoid Arthritis. Preliminary Report. *Proc Staff Meet Mayo Clin* 24:181, 1949.
- Hench P. S. et al. Effects of Adrenal Cortical Hormone 17 hydroxy 11 dehydrocorticosterone (Compound E) on the Acute Phase of Rheumatic Fever. Preliminary Report. *Proc Staff Meet Mayo Clin* 24:277, 1949.
- Hills A. G., Forsham P. H., and Finch C. A. Changes in Circulating Leukocytes Induced by the Administration of Pituitary Adrenocorticotrophic Hormone in Man. *Blood* 3:755, 1948.
- Kendall E. C. Adrenal Cortex. *Arch Path* 32:474, 1941.
- Mason H. L. et al. Results of Administration of Anterior Pituitary Adrenocorticotrophic Hormone to Normal Human Subject. *J Clin Endocrinol* 8:1, 1948.
- Perera G. A., Blood D. W., and Reinhold K. H. 11 Dehydrocorticosterone: Its Effects on Hypoadrenalism in Man. *Am J Med* 1:135, 1948.
- Reifenstein E. C., Jr., Albright F., and Wells S. L. Accumulation, Interpretation and Presentation of Data Pertaining to Metabolic Balances. Notably Those of Calcium, Phosphorus and Nitrogen. *J Clin Endocrinol* 5:367, 1945; correction 6:232, 1946.
- Selye H. Effect of ACTH and Cortisone upon an "Anaphylactoid Reaction." *Canad. M.A.J.*, 61:553, 1949.
- Selye H. General Adaptation Syndrome and Diseases of Adaptation. *J Clin Endocrinol*, 6:117, 1946.
- Selye H. *Encyclopedia of Endocrinology*. Montreal: A. W. T. Franks Publishing Company, 1943.
- Soffer L. J. et al. The Effects of Anterior Pituitary Adrenocorticotrophic Hormone (ACTH) in Myasthenia Gravis with Tumor of the Thymus. *J Mt Sinai Hosp* 15:73, 1948.
- Thorn G. W. et al. Studies on the Relation of Thymus and Adrenal Cortex. *Proc Staff Meet Mayo Clin* 24:277, 1949.
- White A. and Dougherty T. F. Pituitary Adrenocorticotrophic Hormone: Control of Rate of Release of Serum Globulins from Lymphoid Tissue. *Endocrinology* 36:207, 1945.

DISEASES DUE TO PHYSICAL AGENTS

THERMAL STATES

(1) Sunstroke heat stroke insolation
thermic fever hyperthermia siriasis

(2) Heat exhaustion heat shock

(3) Heat cramps

These three conditions are entities calling for distinct treatments but all deriving in some degree from disorder of the heat regulating mechanisms

In the first group the characteristic feature is heat retention with highly elevated body temperature. Treatment is to be directed primarily to temperature reduction. Erstwhile heroic measures of ice packs ice tubing and ice enemas should give way to prompt air cooling cold sponging and moderately cold packs. The higher the temperature elevation the greater the urgency and the warrant for severer chilling. No effort should be made to lower the temperature below 101 to $102^{\circ} F$. Saline or glucose introduction is not indicated. Rarely is artificial respiration required. Pulmonary edema may appear and necessitate control. Rest in the recumbent position should continue for days in more serious instances but with some changes in position. This may obviate subsequent unfavorable developments in which convulsive states may arise.

In the second group heat dispersion dominates with vasomotor collapse calling for treatment. Treatment best suited to mild surgical shock is indicated. Intravenous glucose has been both praised and condemned. Generally treatment is on the basis of symptomatology.

In heat cramps saline depletion notably of muscle tissue with or without accompanying dehydration serves as the basis of the abnormality and determines both therapy and treatment. All patients with moderate or severe heat cramps should be given 2 or more liters of physiologic saline solution. The intravenous route is superior but the ingestion of 0.5 per cent salt solution may

suffice. Intake of the usually available 16 gram salt tablets along with water may meet the situation. Milk because it contains 0.3 per cent of salt in such quantities as a quart may be superior to an equal concentration of saline. Few cases require hospitalization.

Despite clinical dissimilarity these three states will respond to the same forms of prevention. Protective clothing provides no certainty of escape from insolation. The absence of bright sunlight equally guarantees no full safety. In indoor activities much may be gained by scant clothing. In general in hot occupations with or without associated high humidity protection to the extent practical should be sought through mechanical dispersion of hot atmospheres.

More specifically in hot occupations and for all during excessively hot weather healthy persons may profit by a high intake of salt tablets or by the free drinking of salinized chilled water (0.1 or 0.2 per cent). Increased milk drinking may accomplish the same end. If salt tablets are relied on most persons prefer the 0.5 gm. content in friable form. Some are enteric coated because of the nausea sometimes induced.

Once present any one of the three states mentioned tends to recur even at lower exposures. For persons facing this prospect extra preventive measures are justified.

CARY P. MCCORD

REFERENCES

- Helman M. W. and Montgomery E. S. Heat Disease. Clinical and Laboratory Study. *J. Ind. Hyg. & Toxicol.* 18:651 1938.
Marsh F. Heat stroke and Heat Exhaustion. *Brit. Ency. of Med. Practice* 8:396 1937.
Schmidt G. Die Folgen des "Sonnenstichs" am

ps and
In Inst

Work

men J. Indust. Hyg. 10:11 1929

Weiner, J S Experimental Study of Heat Collapse
J Indust Hyg & Toxicol, 20:389 1938

MOTION SICKNESS

Sea Sickness, Air Sickness, Train Sickness, Car Sickness
 Swing Sickness

These conditions sharing common causation likewise share some degree of responsiveness to the same treatment. As a forerunner to statements relative to treatment, it is necessary to mention the four currently accepted bodily sources of such disorders since therapy in some measure may be directed to specific types of motion sickness. These are (1) the vestibular apparatus, (2) abnormal visceral motions, (3) psychic, (4) combinations of the three. The last probably represents the commonest variety.

In therapy and prevention scores of different drugs have been utilized with some degree of success for all. The number includes atropine compounds, bromides, strychnine, benzedrine, hyoscine and its compounds, hyoscyamine, ergotamine, chloroform, thiamine, and the barbiturates. Various of these substances have been applied in combination. At the present time the consensus favors hyoscine or its compounds or in combination with other substances such as acetylsalicylic acid. This drug may be introduced orally or in rectal suppositories, in chewing gum, or through tablets for sublingual absorption. It may provoke mouth dryness and diminished sweating, mild dizziness, and flushing of the skin. These disadvantages when present seldom outweigh the relief frequently provided. For prophylactic and therapeutic purposes, doses recommended have ranged from $\frac{1}{100}$ grain (0.015 mg) to $\frac{1}{400}$ grain (0.06 mg). One commercial product represents hyoscine hydrobromide, $\frac{1}{400}$ grain, mixed with acetylsalicylic acid, 3 to $\frac{1}{2}$ grains, both incorporated in chewing gum tablets. Since gum chewing is a common practice in air flight and somewhat common in sea travel, this approach to therapy is reasonable. Another combination for oral intake in tablet form represents 0.1 mg hyoscine camphorate and 0.4 mg hyoscyamine camphorate. For suppositories the oral dosage is ordinarily doubled. It is good practice to institute motion sickness

prevention 1 or 2 hours prior to departure. Failure to prevent discomfort in this manner may lead to repeated doses at 3 or 4 hour intervals but therapy at this rate should not extend over more than 24 hours. For children over 7, the drug dose is about one half of that for adults, and lower for younger children. The aminoxide hydrobromide is said to be superior to the plain hydrobromide.

A host of physiologic procedures retard air motion sickness. A few are here noted: the wearing of dark glasses or otherwise the avoidance of the viewing of apparently moving objects, the wearing of ear defenders for the purpose of some avoidance of noise, sitting or lying in the line of motion rather than sideways, the avoidance of excessive alcohol or food intake, although light food intake may be favored.*

CAREY P. MCCORD

REFERENCES

- Anon. Critical Study of Seasickness Remedies. *Bull War Med*, 4:306 1944.
 Anon. Preventing Air Sickness. *Science News Letter* 42:378 1942.
 Damrau F. Motion Sickness and Its Relief. *M Rec*, 160:408 1947.
 Hemingway, A. Relationship of Air Sickness to Other Types of Motion Sickness. *J Aviation Med*, 17:80 1946.
 Holling H E, McArdle B, and Trotter, W R. Prevention of Seasickness by Drugs. *Lancet*, 1:127 1944.
 Lishenthal J L, Jr. Effect of Hyoscine on Airsickness. *J Aviation Med*, 16:39, 1945.
 Monto R W. Treatment of Motion Sickness. *J Michigan M Soc*, 46:1184, 1947.
 Noble R L, Sellers E A, and Best C H. Treatment of Motion Sickness (Review of Therapeutic Studies Sponsored by National Research Council of Canada). *Canad M A J*, 56:417, 1947.

* Recently Gay and Carlsner have described a new drug, b-dimethylaminoethyl benzhydryl ether 8-chlorotheophyllinate, as being effective in seasickness and motion sickness. This drug marketed under the trade name of dramamine received extensive trial by the Army during the last war and was successful in preventing the distressing symptoms of seasickness. The dosage is 100 mg before each meal and at bedtime. It now appears to be the drug of choice in all types of motion sickness.—Editor

Gay, L N, and Carlsner, P E. The Prevention and Treatment of Motion Sickness. *Bull Johns Hopkins Hosp*, 84:470, 1949.

MOUNTAIN SICKNESS

{Air Sickness}

Man's diseases, and correspondingly treatment therefor, at high altitudes distinctly are influenced by his rate of ascent, energy expenditures in the process, and the total elapsed time (acclimatization) involved. Manifestly, rapid decompression and fast motion characteristic of other forms of "air sickness," do not occur in "mountain sickness." Oxygen intake so essential both for prophylaxis and cure for anoxia in connection with high altitude aviation, is far less serviceable or usable in mountain sickness. The prime therapy of mountain sickness is on the physiologic level and centers about acclimatization, with a different acclimation requirement for every significant increase in elevation. Without medical influence, the body adapts itself through readjustments to modified tensions of carbon dioxide, oxygen and to altered respiratory rate and excursion. The number of red blood cells significantly increases and physical exercise becomes increasingly burdensome. Alkalosis makes its appearance.

For the sick and the frail, medical cure may be required at even the 5000 ft level. Scant exercise is in order. Intermittent oxygen intake may be provided, although this procedure may interfere with physiologic readjustments. Mental and emotional states may suggest mild sedation, but psychotherapy may be more commendable. At the 14000 ft level the highest reached by any large number of individuals in this country (Pike's Peak), a fair percentage of visitors presents genuine mountain sickness in which panic or at least fright is a frequent feature. Obviously this means that physicians throughout the country are consulted by those planning any such excursions into the higher regions. His advice for the unadvised should emphasize minimal exertion, if practical periods of inurement at lower level, the avoidance of panic, recognition of prospects of impaired judgment, and possibly trivial sedation. Clearly certain physical states such as pronounced emphysema, should preclude or deter any such ascents. The return of the acclimated person to levels below 1000 ft may be accompanied by some what similar discomfort which again re-

solves on the basis of physiologic adjustment with time as a factor.

CAREY P. McCORD

REFERENCES

Henderson, Y. *Adventures in Respiration: Modes of Asphyxiation and Methods of Resuscitation* 1919

Le

Le

DECOMPRESSION DISEASE

Caisson disease has emerged from the aquasphere and in reverse fashion has entered the stratosphere. This classical term should give way to or be associated with others such as "aero embolism," "compression disease," "decompression disease," "bends," etc. Wherever encountered, the condition derives from the formation of nitrogen bubbles in the tissues or joint spaces wholly unexpected in man's normal gaseous balance at the earth's surface. In stratospheric occurrence, anoxia, low temperatures, and occasionally gravitational abnormalities confuse but do not directly enter the situation.

All treatment is prophylactic or physical. The fundamental requirement is to prevent the formation of the nitrogen bubbles or to get rid of them. High altitude (above 3000 ft, 226 mm Hg) flying requires for pilot pre periods of moderate exercise with increased intake of oxygen to reduce nitrogenation of tissues together with gaseous elimination from the intestinal tract, etc. For passengers, pressurized aircraft is requisite to flight beyond readily predetermined altitudes. Descent to lower levels may ameliorate symptoms, but reascend accentuates manifestations, apparently from expansion of nitrogen bubbles not fully dispersed. Individual susceptibility is pronounced.

In underwater work in which hard labor may be performed under several multiples of normal atmospheric pressure and for relatively prolonged periods, caisson disease or bends is inevitable unless slow, regulate somewhat standardized decompression is instituted in ascent. Failure to obviate it

disease requires prompt recompression in surface chambers designed for that purpose or otherwise actual resubmersion. Oxygen intake in surface chambers is desirable. Artificial atmospheres with helium substituted for nitrogen promises to diminish the perils of caisson exposure, since helium disperses much more readily than nitrogen. At times treatment with inhalators furnishing 20 per cent oxygen and 80 per cent helium may prove more satisfactory than pure oxygen.

of a visible water line through the tympanum or other significant signs may be expected to recover without specific treatment within 6 weeks provided further exposure insult is avoided.

Aerodentalgia a common feature of air travel and presumably chiefly due to expanding gas bubbles may justify the use of analgesics. Comfort usually is restored on landing. Otherwise or if repeatedly disturbing in flights dental care should be obtained.

CAREY P. McCORD

REFERENCES

- Armstrong H G *Principles and Practice of Aviation Medicine* Baltimore: Williams & Wilkins Company 1943
- Barach A L et al Effect of Ammonium Chloride on Altitude Tolerance *J Aviation Med* 17 123 1946
- Bauer L H *Aviation Medicine in Oxford Medicine* 1 543 New York: Oxford University Press 1943
- Behnke A R Concepts Derived from Investigations Pertaining to High Altitude Flight *JAMA* 133 450 1947
- Be
- Be
- Wilkins Company 1943
- Carson L D Ocular Effects of Altitude Flying and of Deep Sea Diving *Arch Ophthalmol* 33 173 1945
- Government Publication *Outline of Course of In-*
- Submatters *Ann Otol Rhin & Laryng* 55 347 1946

Pre-flight Oxygen Breathing in Preventing Decompression Sickness *J Aviation Med* 16 350 1945

James C C M Late Bone Lesions in Caisson Disease: 3 Cases in Submarine Personnel *Lancet* 2 6 1945

Knitler R A Acute High Altitude Anoxia: Gross and Histologic Observations in 27 Cases *War Med* 6 369 1944

McFarland R A Effects of Oxygen Deprivation (High Altitude) on Human Organism *Civil Aeronautics Authority Tech Div Report* 11 Washington D C 1938

Rodbard S Occurrence of Decompression Sickness on Descent from High Altitudes *J Aviation Med* 17 89 1946

Schuessler C Effect of High Altitude on Oral Tissues *Mil Surgeon* 100 318 1947

Taylor H K Aseptic Necrosis and Bone Infarcts in Caisson and Non-caisson Workers *New York State J Med* 43 2390 1943

Van Der Aue O E Duffner G J and Behnke A R Treatment of Decompression Sickness: Analysis of 113 Cases *J Indust Hyg & Toxicol* 29 359 1947

ELECTRIC SHOCK

Electric injuries occur with such wide variation in site and severity that suitable therapy may not be anticipated for every situation. In general requirements of treatment fall into three categories: (1) emergency care immediately following the rescue of the victim; (2) surgical care of external injuries usually burns; (3) care of early or late sequelae should any appear. Opportunities for sequelae are legion. These may range from slowly developing cataracts to traumatic neuroses.

In this publication consideration may be directed only to the first item. Assuming that the electrically shocked individual has been removed from further exposure and has not suffered other injuries for example from falls, three items require appraisal: (1) The patient may be unconscious and not breathing. Manual artificial respiration should be administered promptly, with preference at this time for the Schaefer method. Resistance to the resumption of breathing by a viable person may be great. The use of oxygen or oxygen dioxide mixtures is indicated. Mechanical artificial respiration is to be con-

done only if conducted by skilled operators. In the absence of restored breathing some form of artificial respiration should be continued until rigor mortis indicates defeat. (2) During artificial respiration or in its absence if unnecessary, surgical shock may be present or imminent. The same therapeutic procedures that apply to any surgical shock are suitable here and the same urgency exists. (3) A common major critical threat in electrical shock is ventricular fibrillation. It is thought by some that ventricular fibrillation in electric shock may not be quite so fulminating as ventricular fibrillation in some other states. Even so there is scarcely opportunity for therapy. Under laboratory conditions countershocking through the chest wall with currents at 30 ampere levels may be efficacious. The introduction of 2 cc of potassium chloride (0.5 per cent) into the arterial system followed by a solution of 10 cc of calcium chloride (0.023 gm) may likewise control ventricular fibrillation. Obviously neither procedure is practical for the electric shock emergency. Johnstone has suggested that acetyl methylcholine chloride in small doses might be considered for the control of fibrillation. It appears unlikely that epinephrine serves other than harmful purposes in this cardiac state.

should be kept in bed for 1 to 2 weeks. Judicious treatment during this period may ward off latent effects either emotional or organic.

CAREY P. McCORD

REFERENCES

- Best, C. H. and Taylor, N. B. *Physiological Basis of Medical Practice*. Baltimore: W. B. Saunders Company, 1943.
- Petersen, A. (Editors). *Legal Medicine and Toxicology*. Philadelphia: W. B. Saunders Company, 1923.

CARBON MONOXIDE ASPHYXIA

The single action of carbon monoxide is on the hemoglobin, robbing that tissue of its oxygen-carrying power. Consequently, the

essence of treatment centers about the removal of carbon monoxide from its association with hemoglobin. In less severe cases, carbon monoxide, obeying the laws of gases, rapidly dissociates spontaneously but even these milder involvements should not be accompanied by any unnecessary expenditure of the patient's energy. Effort exaggerates symptoms. In more severe instances after removal from further exposure the patient should be subjected to the best available means for promoting pulmonary ventilation. Only infrequently does respiration cease in a viable person but artificial respiration may be required. It is always possible to institute manual artificial respiration employing the method of choice of the physician. If at all available and as rapidly as possible the inhalation of oxygen should be instituted either in connection with the patient's breathing or with artificial respiration if required. Mechanical artificial respiration is fraught with some dangers, notably if conducted by poorly trained laymen. The mask of the oxygen inhalator should not be strapped over the face since undetected vomiting may lead to drowning. Except in the mildest of carbon monoxide asphyxia oxygen inhalation if available is beneficial and should be employed even though the patient appears to be in good condition since its use frequently and promptly eliminates disturbing manifestations such as headaches. Superior to oxygen alone is oxygen mixed with carbon dioxide at the 5:7 or 10 per cent level of the latter. Availability commonly determines the percentage. Carbon dioxide serves as a respiratory stimulant and promotes pulmonary ventilation. Coma ordinarily appears when the blood saturation with carbon monoxide is near 40 per cent above 60 per cent death is imminent. Within the zone of 40 to 60 per cent the prompt utilization of oxygen-carbon dioxide mixtures readily may reduce the saturation percentage by 50 per cent within 30 minutes or 1 hour. During this early period the patient

within the chest. During this stage it is commonly true that some dilatation of the heart exists; therefore the patient should be kept quiet and warm. The intake of oxygen or

REFERENCES

- Drinker C A. *Carbon Monoxide Asphyxia*. New York: Oxford University Press, 1938.
 Johnstone R T. *Occupational Medicine and Industrial Hygiene*. St. Louis: C. V. Mosby Company, 1948.

ATOMIC RADIATION INJURIES

The
 duced
 are not

grosser secondary effects resulting in changes in the various organ systems of men and animals have been observed for a period long enough to permit an approach to the treatment of injuries produced by ionizing radiations.

The radiations released in nuclear fission cover the entire spectrum of radiant energy from gamma rays through infra red. They include neutrons, protons, alpha particles, electrons, and the radioactive products of fission of plutonium or uranium in the case of an atomic bomb explosion as well as plutonium or uranium which has not undergone fission. These radiations and radioactive elements may affect the body by irradiation of the surface or following ingestion or inhalation of particulate radioactive materials by irradiation of the internal environment.

The effects of these radiations manifest themselves clinically for the greatest part in changes in the hematopoietic system, the digestive tract, skin and gonads. Roughly stated, the clinical course following radiation injury depends on primary cellular injury and secondarily from continued injury from absorption of toxic substances of an ill defined nature and bacterial infection.

Studies conducted on survivors of the Hiroshima and Nagasaki exposures would seem to indicate that all persons exposed to 100 roentgens of total body radiation or less will survive. Those exposed to from 100 to 300 roentgens will be seriously damaged but may live if properly and vigorously treated, whereas those subjected to more than 300 roentgens will almost certainly die in spite of detailed application of known therapeutic measures.

The extent and nature of the injury sustained are dependent on certain factors. These include the total quantity of radiation

oxygen-carbon dioxide mixtures should be continued for longer periods represented by hours but tapering off with intermittency. If blood samples have been collected (usually after reaching the hospital) these eventually indicate minor percentile saturation. It may not be necessary to continue oxygen inhalation solely for the purpose of eliminating these residual traces. The usual tobacco smoker may yield evidence of 2 to 4 per cent of blood saturation and without symptoms of known significance. After the period of emergency treatment the patient without physical effort on his own part should be hospitalized as symptoms tend to recur calling for further inhalation therapy. Resort to drugs is usually futile. Guarded exception may be made in favor of 7½ grains (0.5 gm.) of caffeine sodium benzoate and coramine (pyridine β carboxylic acid diethylamide) 1 cc intravenously. Drug production subcutaneously is less effective because of the impaired circulation.

While chronic carbon monoxide poisoning is a misconception, chronic exposure is well established. So called "chronic poisoning" customarily represents repeated acute episodes or the sequelae of gross acute poisoning. Sequelae on an organic basis are not to be expected unless the acute stage has been severe as reflected by coma or near coma extending into 3 or 5 hours duration. The nature and site of organic sequelae are unpredictable but all stem from anoxia. Any organ or tissue may be involved. The range may extend from minor persistent headaches to optic atrophy, psychopathic states or gangrene of a member. Manifestly, treatment of sequelae be they early or late must be adapted to the individual situation.

Carbon monoxide victims are peculiarly prone to subsequent psychoneurotic states. From the beginning the physician ministering to a conscious patient both negatively and positively should seek to fend off provocations to neuroses. Apart from the requirements of the early emergency situation possibly the most difficult of therapeutic tasks on the part of the physician is to protect the carbon monoxide victim against functional disorders. When neuroses arise therapy in novise departs from that suitable to such disorders from any other source.

CAREY P. MCCORD

to which the body is exposed, part of the body exposed, the types of radioactive particles affecting the body, and the energy of the particles and radiations. As an example, the neutron has a "biologic effectiveness" or capacity for damaging tissue from 10 to 20 times that of gamma radiation, whereas very "long" or "soft" secondary roentgen rays have a destructive capacity of roughly 1/10th that of gamma rays.

The treatment of casualties of an atomic bomb explosion is complicated by the multiplicity of the nature of the bodily damage. In addition to the acute and late radiation effects, there are those of solid blast, thermal, infra red, and ultraviolet burns, and trauma from falling structures. The treatment of these depends, of course, on well established principles of traumatic surgery and medicine. These include the alleviation of the shock-like state induced by the aforementioned factors. Recent studies indicate the importance of the rapid elimination of inhaled or ingested radioactive substances from the body. A means for accomplishing the partial elimination of plutonium and radiostrontium in experimental animals has been devised. The treatment of an acute shocklike state is that of traumatic shock from any cause: early and generous administration of plasma plus adequate sedation. Definitive treatment of burns with sterile pressure dressings and débridement of traumatic wounds is of utmost importance because of the subsequent interference with immune mechanisms. The surface of the body and wounds themselves must be decontaminated from radioactive materials by appropriate means if they are found to be present.

Damage to the epithelium of the entire gastro-intestinal tract leads, on the second to seventh day after severe radiation exposure, to marked loss of electrolytes and body fluids. Close attention should be given to the restoration of fluid and electrolyte balance. Leukopenia appears rapidly after radiation damage. A disappearance of circulating lymphocytes is promptly seen followed in a day by a loss of granulocytes, depending in its degree on the severity of radiation exposure. Within a few days following the appearance of this leukopenia, clinical manifestations are seen similar to those present in an acute agranulocytic angina, involving

the pharynx, tonsils, and mucosae of the mouth and nose. Vigorous and prolonged use of the antibiotics, penicillin and streptomycin, parenterally and the sulfonamides if renal function permits, is a necessity until the immune mechanisms, including a return of the white blood count to normal, are re-established.

Following radiation damage of moderate to severe degree, purpura and other hemorrhagic manifestations may appear from the fourth to 14th day. A marked decrease in the number of platelets in the peripheral blood occurs. Concomitant with this a progressive increase in a circulating "heparin like" protamine titratable substance appears which inhibits the clotting mechanism. Moreover, eventually a rapidly progressive anemia, dependent on both blood loss and failure of the erythropoietic mechanism, appears.

Repeated transfusions of whole blood in

require approximately 25 liters of blood administered during the first several weeks after exposure and that the administration of blood will, on the average, be prolonged for as long as 8 to 12 weeks. Transfusions should begin before a decided fall in the red blood count is apparent.

The parenteral administration of protamine sulfate and toluidine blue has been effective in combating the hemorrhagic manifestations in dogs accompanying the appearance of the circulating heparin like substance. A suggested regimen for the administration of these drugs in man is the use of 6 to 8 mg of toluidine blue per kilogram of body weight dissolved in a physiologic solution of saline and administered intravenously over a period of 2 hours daily for 11 days, followed by half this dose on subsequent days. Protamine sulfate may be given intravenously in dosage of 150 mg in saline solution over an hour's period, accompanied by 50 mg in 5 ml aqueous solution intramuscularly. This is followed by the same dosage intramuscularly every 4 to 11 hours until the protamine titration returns to a normal level of 0.140 mg of protamine.

In general practice it is extremely difficult to determine the presence of plutonium or

other radioactive substances within the body except by elaborate physicochemical procedures. However, assuming that this is practicable and that plutonium or radioyttrium is demonstrated in the body or is known to have been incorporated into the body parenterally or through the digestive or respiratory tract then it is important that these substances be eliminated as rapidly as possible. By continued irradiation of the site of their deposition these substances induce late neoplastic changes.

It has been shown that the intravenous administration of zirconium citrate results in

mental animal have shown that following a long latent period of many months to years plutonium stored in the bone results in the production of osteogenic sarcomas. Animal experiments indicate that the therapeutic use of zirconium citrate may be a valuable addition to the armamentarium available in the treatment of persons exposed to plutonium and radioyttrium. The present state of development in this field does not as yet permit of definitive dosage schedules for the human.

In summary the therapy of radiation injuries includes the vigorous primary treatment of the acute shocklike state maintenance of fluid and electrolyte balance decontamination of the body's surfaces of both bacterial and radioactive contaminants prolonged administration of antibiotics early and adequate use of whole blood transfusions and the administration of protamine sulfate and toluidine blue for the control of

intravenously in known cases of plutonium or radioyttrium poisoning may be of great importance.

ROBERT J. HASTERLIK

REFERENCES

- Allen J G et al A Protamine Titration as an Indication of a Clotting Defect in Certain Hemor
1947
- Beck J M P and Meissner W A Atomic Bomb Surface Burns Some Clinical Observations Among Prisoners of War Rescued at Nagasaki Kyushu J Indiana M A 40 515 1947
- Brues A M With the Atomic Bomb Casualty Commission in Japan Bull Atomic Scientists 3 143 1947
- Brues A M Lisco H and Finkel M P Carcinogenic Action to Some Substances which May be a Problem in Certain Future Industries Cancer Research 7 48 1947
- Brues A M et al General Report Atomic Bomb Casualty Commission January 1947 Report on the Medical Studies of the Effects of the Atomic Bomb by Dr Masao Tsuzuki Professor of Tokyo Imperial University pp 66-112 Washington D C National Research Council 1947
- Cantril S T Jacobson L O and Nickson J J
Cronkite E P The Diagnosis of Ionizing Radia
Leucutha T Radiant Energy Injuries Am J Roent
of Zirconium and Sodium Citrate Treatment on the Metabolism of Plutonium and Radioyttrium J Lab & Clin Med 34 313 1949
- Stone R S The Plutonium Project Radiology 49 364 1947
- Warren S and Draeger R H Pattern of Injuries Produced by Atomic Bombs at Hiroshima and Nagasaki U S Nav M Bull 46 1349 1946

DISEASES DUE TO INTOXICATIONS

ACUTE ALCOHOLISM

Symptoms of acute alcoholism have been correlated in recent years with blood alcohol concentrations and there is good evidence that the values obtained from the blood are identical with the concentration in the brain. The rapidly established equilibrium between the blood alcohol and the alveolar air permits the use of expired air for alcohol determinations (Ellerbrook and Van Gaasbeek, Muehlberger). Usually blood concentrations of 0.05 per cent (0.5 mg per cubic centimeter) are considered harmless. Three times this concentration is already harmful and is considered as evidence of intoxication, with 0.25 per cent gross lack of coordination is obvious, 0.4 per cent produces deep and possibly fatal coma. The increased tolerance of the habitual drinker is not completely understood, but probably is based on tissue tolerance and psychic factors rather than on a difference in the ability of the body to handle the alcohol.

Alcohol is rapidly absorbed even from the stomach and the average person can oxidize about $\frac{1}{2}$ oz per hour if moderate amounts have been taken, thus 4 oz of whiskey or 10 times as much beer will be eliminated in 5 to 6 hours. The congeners of ethyl alcohol, the so called "fusel" oils which are present in poorer grades of liquors (up to 0.5 per cent),

increase or no

Jellinek, Haggard et al.)

The physician will be called on to treat acute alcoholic poisoning only in severe cases. Many forms of treatment have been recommended and it is impossible to discuss all of them. In the following, a number of procedures are described which should be useful not only for the various forms of alcoholic intoxication, but also to give the physician an opportunity to select the method most suitable to the individual circumstances

under which he has to attend his patient.

The acute alcoholic attack of the occasional heavy drinker or a sudden exacerbation of the chronic alcoholic in uncomplicated form will frequently confront the physician with a boisterous, hard to manage patient. In the absence of manifestations indicating impending delirium tremens or of evidence of organic illness, particularly of the heart, or severe malnutrition we have seen prompt success from the subcutaneous administration of $\frac{1}{2}$ o grain (6 mg), of apomorphine hydrochloride. This is followed within a few minutes by nausea, vomiting and a marked sedative effect. Frequently this procedure will be enough to sober the patient up and bring him out of the acute phase. In cases where this treatment is not necessary or is inadvisable, vomiting should be induced by mechanical means, if possible. Sedation is frequently required and should be induced by paraldehyde, by mouth mixed in cold fluid, or rectally in a thin starch suspension.

The initial dose has to be varied according to the individual patient and is usually between 8 and 20 cc. This can be followed by additional doses of 8 cc at 1 or 2 hour intervals, if needed. Paraldehyde can be injected intramuscularly in doses of 10 cc, intravenous administration should preferably be avoided (Chapman). While paraldehyde is preferred by most authors barbiturates may be useful. Morphine should be avoided in this condition. The patient should be encouraged to take fluids as soon as possible particularly fruit juices and sugar. Thiamine hydrochloride can be administered in doses of 25 to 50 mg by mouth or by injection. The judicious use of apomorphine 10 mg, mornings and at noon helps sometimes to shorten the subjective symptoms of the hangover period (Millet). Analgesics may be administered and a barbiturate given for the night because sleep is an important factor for recovery.

Acute alcoholic psychosis characterized by temporary complete disorientation impending or fully developed delirium tremens with hallucinations requires frequently a more prolonged treatment. The long disputed theory that delirium tremens is due to sudden withdrawal of alcohol has been abandoned. Today many physicians favor abrupt withdrawal of alcohol but others still believe in a more gradual procedure.

Most of the modern schemes of treatment are built around ample administration of fluids and carbohydrates first intravenously if necessary and later orally and the injection of insulin either in relatively small doses or in larger ones with the intent of producing definite hypoglycemia.

While there are experimental data demonstrating that insulin hastens the oxidation of alcohol in animals and man these claims have been disputed by some investigators. The majority of clinical investigators believe such procedures to be of definite value.

A treatment scheme which is relatively simple to conduct and which provides for a gradual withdrawal of alcohol begins with the intravenous injection of 50 cc of 50 per cent dextrose together with 10 units of insulin and 1 cc of an injectable vitamin B complex solution (Nason). This procedure may be repeated up to five times at 4 hour intervals if necessary. After the acute phase has passed the patient is given 2 oz of whisky diluted with 8 oz of water. This is repeated at 3 hour intervals for five doses. Three more such drinks are suggested but

the patient should be encouraged to resume salted foods because the blood chlorides are frequently lowered in this condition. Usually the patient should be mentally clear in 30 to 33 hours except in severe cases which require prolonged treatment in the hospital.

A somewhat different procedure does not provide for any alcohol administration but uses higher doses of insulin to cause definite hypoglycemia and accordingly requires careful medical supervision (Robinson). The patient is given 20 units of insulin subcutaneously on admission and encouraged to take 30 oz of orange juice during the next 3 hours. This is followed by a second injection of 20 units of insulin. Usually the first dose

causes hunger and ample carbohydrates are given. Most patients quiet down and fall asleep within an hour or two after the second injection. Otherwise a third dose of insulin may be given 3 hours after the last one with carbohydrates by mouth or if necessary 500 cc of 10 per cent dextrose by intravenous infusion. This treatment may be repeated as a whole or in part if the patient is not clear within 5 hours after he awakens from his sleep. Usually recovery occurs in 36 hours. Insulin shock should be prevented and will not occur if the patient is watched and carbohydrates are taken in adequate amounts.

These procedures can be supplemented by sedation with paraldehyde or barbiturates if required and administration of thiamine hydrochloride. Amphetamine, desoxyephedrine or dexedrine can be used to combat mental depression as mentioned above.

Tepid baths are also recommended as helpful in quieting excited patients.

In the severest cases of acute alcohol intoxication the patient will be found in profound coma and energetic methods will have to be instituted. It should be remembered that alcohol is not infrequently used as a carrier for other poisons as for instance barbiturates or the patient may also suffer from an endogenous condition. Blood alcohol determination will be helpful in such cases.

should include inhalation with carbon dioxide because this gas has been shown experimentally to increase the tolerance to otherwise fatal concentrations of alcohol. Analeptic drugs as metrazol, nikethamide (coramine) or picrotoxin are of symptomatic value. The last named drug needs some skill for safe and effective administration (see under Barbiturate Poisoning) (Moore). Intravenous (10 to 15 mg) and later intramuscular injections (15 to 30 mg) or desoxyephedrine (desoxyn, methedone) at intervals of 1 hour can be tried. Blood pressure and heart action should be watched especially in older persons.*

RICHARD K. RICHARDS

* Recently administration of meprobene (known under the trade names miltaine, tolserol or lisephen) has been suggested on the basis of work

REFERENCES

- Chapman, C. B. *Delirium Tremens* New England J Med, 231 249, 1944
- Elletbrook L. D., and Van Gaasbeek, C. B. *Rehabilitation of Chemical Tests for Alcoholic Intoxication, Importance of Selection and Proper Material for Analysis* JAMA 122 998, 1943
- Haggard, H. W. and Jellinek E. M. *Alcohol Explored* New York Doubleday & Company, 1947
- Haggard H. W. Greenberg I. A., and Cohen L. H. *The Influence of Congeners of Distilled Spirits upon Physiological Action of Alcohol* Quart J Stud on Alcohol, 4 3 1943
- Müller M. M. *Amphetamine Sulfate in Aborting Acute Alcoholic Cycle* Am J Psychiat, 100 800, 1944
- Moore M. *Treatment of Alcoholism* New England J Med 221 489, 1939
- Muehlberger C. *Scientific Tests in Evidence Chemical Tests for Alcoholic Intoxication* Am Pract, 1 360 1947
- Nason Z. M. *Safe Method of Detoxicating Acutely Ill Alcoholic* Quart J Stud on Alcohol, 8 43 1947
- Robinson G. W. *Treatment of Delirium Tremens with Insulin in Subshock Doses* Am J Psychiat, 97 186 1940

POISONING WITH METHYL ALCOHOL (METHANOL)

This dangerous substance, also called wood alcohol is frequently used for industry by Schlann and Unna. Doses of 0.5 to 1 gm four times daily are said to be useful in promoting sedation and relaxation as well as decreasing anxiety and tremor. This treatment may be used supplementing other procedures and may reduce the amount of barbiturates used in some of them. While some authors have already given as much as 3 gm of this drug every 4 hours for 2 days or even administered it intravenously, it is advisable to await further confirmation of the usefulness and safety of this regimen before it can replace proved schemes.

Both the anterior pituitary adrenocorticotrophic hormone (ACTH) and adrenocortical extract (ACE) have been recently studied in the treatment of Korsakoff's psychosis, acute alcoholic intoxication and delirium tremens. Both hormones seem to be about equally effective in the treatment of acute alcoholic intoxication. ACE having a greater sedative effect and ACTH affecting anorexia more rapidly. ACE was given some preference in this condition because of its greater sedative action. On the other hand ACTH was more effective in the treatment of delirium tremens than ACE. These are initial results which demand further verification and experience.—Editor

- Schlann, L. S., and Unna K. *Some Effects of Myanesis in Psychiatric Patients* JAMA, 140 672, 1949
- Smith, J. J. *The Treatment of Acute Alcoholic States with ACTH and Adrenocortical Hormones* Quart J Stud on Alcohol, 11 119, 1950

trial and other purposes and poisoning has occurred with materials which do not immediately suggest the presence of methyl alcohol. Inhalation of the vapor is likewise dangerous. The acute fatal dose of methyl alcohol in animals is greater than with ethyl alcohol, but the overall toxicity of methyl alcohol is much greater. One reason for this is its extremely slow oxidation, a single large dose may take a week for detoxification. Formaldehyde and formic acid are assumed to be two of its oxidation products and it is believed by many writers that these highly toxic chemicals are at least partly responsible for some of the toxic effect, as, for instance the well known impairment of vision. Increased formic acid excretion in the urine has been shown to occur in severe methyl alcohol poisoning (Lund). Individual susceptibility to methyl alcohol varies greatly, and while usually 100 to 150 cc are considered fatal for an adult doses as low as 50 cc have occasionally been reported to have resulted in fatalities. The same variation exists regarding the damage to the eyes but in some persons permanent blindness has resulted from as little as 10 cc. The early symptoms of methanol poisoning may be mistaken as being caused by ethyl alcohol. However, certain symptoms, as marked abdominal pain, weakness and visual disturbances, dyspnea with marked cyanosis and lowering of blood pressure are suspicious signs. Death may occur quickly, or the patient may linger on for a few days. The death rate is much higher than with ethyl alcohol. The fatal blood concentration for methyl alcohol is similar to that of ethyl alcohol namely, about 0.5 per cent. Treatment should be vigorous and carefully supervised. One of the main objectives is to combat the marked acidosis which develops quickly (Chew et al). The stomach should be emptied and a saline laxative administered, if necessary by stomach tube. This is followed by 1 gm of sodium bicarbonate orally. Four 40 cc ampules of sodium lactate molar solution are added to a liter of isotonic Ringer solution and administered by intravenous drip. If sodium lactate is not available, a 5 per cent solution of sodium bicarbonate freshly prepared by dissolving 1.25 gm. of sodium bicarbonate in 250 cc. of sterile Ringer solution (do not autoclave) can be

given instead. The effect on the alkali reserve is tested by determining plasma carbon dioxide combining power before and after the administration of this solution. If facilities for this are not available the urinary pH may be used as a guide. This treatment is continued by intravenous infusion and by oral doses of 2 gm of sodium bicarbonate at 1 or 2 hour intervals until the carbon dioxide combining power is normal or the urinary pH has reached approximately the value of 7. Sodium bicarbonate should be discontinued after the urinary pH has reached 7.8. This may take several days. Similar therapeutic schemes suggest starting with 1000 cc of 5 per cent dextrose solution in which 15 gm of sodium bicarbonate have been dissolved. This solution is infused intravenously for 1 hour and repeated every 6 hours. Oral sodium bicarbonate 15 gm every 2 hours is given until the urinary pH is 7.0 which is then maintained at this level (Jacobson). Further supportive treatment consists of administration of vitamin B complex and carbohydrate rich foods. The acute stage may require lowering of the intracranial pressure by spinal puncture if indicated and the injections of stimulants in case of severe collapse. Administration of ethyl alcohol has been recommended on the basis of theoretical considerations by Scandinavian authors but actual clinical evidence for this treatment is lacking.

Higher Alcohols. As a rule the acute toxicity of these alcohols increases with the molecular weight. Of greatest practical importance is the isopropyl alcohol which is also used as rubbing alcohol. Small amounts as for instance 20 cc diluted with water have caused no significant effects. Larger doses lead to a state of alcoholic intoxication similar to severe ethyl alcohol poisoning with coma sometimes accompanied with convulsive manifestations. Isopropyl alcohol is partially oxidized to acetone. Treatment is symptomatic and should include intravenous glucose saline or lactate Ringer solutions in severe cases.

n-Butyl alcohol in a mixture with esters has been reported to have caused damage to the cornea and liver.

Isobutyl alcohol is the main constituent of the so-called "fusel oils." It is more toxic than ethyl alcohol but as described above

the small amounts contained in cheap liquors do not significantly affect their toxicity. Treatment is symptomatic and should take into account the slower oxidation of many of these alcohols as compared with ethyl alcohol.

RICHARD K. RICHARDS

REFERENCES

- Chey W B et al Alkali Treatment of Methyl Alcohol Poisoning *JAMA* 130 61 1946
 Jacobson H M et al Acute Methyl Alcohol Poisoning Report of 18 Cases *U S Nav M Bull* 44 1099 1945
 Lund A Excretion of Methanol and Formic Acid in Man after Methanol Consumption *Acta Pharmacol et Toxicol* 4 205 1948
 Roe O Clinical Investigations of Methyl Alcohol Poisoning with Special Reference to the Pathogenesis and Treatment of Amblyopia *Acta med Scand nav* 113 558 1943
 Solimann T H *A Manual of Pharmacology and Its Application to Therapeutics and Toxicology* Philadelphia W B Saunders Company 1948

BARBITURATE POISONING

The incidence of barbiturate poisoning has increased continuously with the popularity of these drugs with the medical profession and the public. In a review of poisonings which the author made for the years 1938-1939 on the basis of the records of the Cook County Hospital in Chicago the barbiturates occupied second place in frequency and were surpassed only by alcohol. The mortality was 65 per cent. According to the Metropolitan Life Insurance Company 55 per cent of fatal accidental poisonings were due to barbiturates in the early 1930's.

It is probable that barbiturate intoxication may be the sole or contributory cause of coma if a patient is found under suspicious circumstances. The combined ingestion of barbiturates with other drugs especially alcohol or opiates may complicate the issue both from a diagnostic and therapeutic viewpoint. Since legal questions are frequently involved the physician will do well to make a careful survey of the circumstances under which the patient has been found, look for empty containers and preserve if possible the contents

of glasses as well as stomach washings and urine. These containers should be properly sealed, marked for identification and sent to a competent toxicologist at once. Modern chemical methods of detection will enable an expert to give the attending physician a quick reply regarding the presence of barbiturates. However, a negative test does not necessarily exclude the possibility of a barbiturate poisoning.

Our discussion will be concerned only with the treatment of subacute barbiturate poisoning which follows the accidental or much more frequently suicidal overdosage with these drugs. We will not consider the management of acute respiratory depression as it may occur during intravenous barbiturate administration.

The question of the so-called minimal lethal dose of the various barbiturate derivatives has been repeatedly discussed but in the light of his experience and a critical survey of the literature it appears to the writer that the determination of such a dose is almost impossible and certainly of little value for the physician who wants to assess the prognosis of an individual case. This is especially true since frequently the amount taken is not known. The often quoted statement that death will usually occur if 15 or more times the average therapeutic dose of a particular barbiturate has been taken can still be used as a rough guide. But this assumption has to be greatly modified according to the circumstances. Unfavorable influences are old age, obesity, organic diseases and a long interval between the ingestion of the drug and the institution of proper treatment. Combined poisoning with other depressant drugs, especially opiates or large doses of alcohol, are likewise aggravating factors.

The onset of symptoms and the rapidity of their progress depend on numerous factors such as the dose and type of drug used, whether it is taken alone or with alcohol and the amount of food present in the digestive tract. In the great majority of cases the effects usually begin after half an hour and are followed by a gradually increasing depression which leads to deep coma with complete areflexia, impaired respiration and sometimes to death due to general depression, pulmonary complications or cerebral

edema after 3 or more days. Pulmonary complications may still be fatal after the patient is already recovering from the barbiturate coma. In rare cases, however, fatal depression may occur within an hour as the result of respiratory paralysis, especially if large doses of the fast acting barbiturates or sodium salts (the commonly marketed form) are taken. Under such circumstances the diagnosis will usually be made too late for effective treatment.

Numerous therapeutic measures and antidotes have been recommended for the management of subacute barbiturate poisoning. It should be stated that patients who have taken only a slight overdose of barbiturates and are found in a condition of mild depression will commonly recover with some supportive treatment without the need for rigorous measures if they show good color, normal blood pressure and respiration and react to stimuli. It must be emphasized, however, that even such patients need close supervision in order to detect any deepening of the coma which may occur owing to absorption of the drug still present in the intestinal tract. For this reason a stomach lavage, either with plain water or a 1:5000 solution of potassium permanganate, should be performed on all patients with care to avoid aspiration. Emetics, either orally or parenterally, should not be given to the depressed individual. After the gastric lavage a laxative dose of sodium sulfate or sodium phosphate should be left in the stomach to hasten elimination. Severe cases of barbiturate poisoning, which are characterized by depressed, slowed respiration (frequently accompanied by gurgling sounds due to accumulated mucus), cyanosis, cold clammy skin and low blood pressure, need careful attention. A quick check of the reflexes is helpful in determining the depth of coma. This may be considered severe if there is no response to painful stimuli if the corneal reflex or the response of the pupil to light is absent or sluggish. While we cannot discuss diagnostic methods in detail in our own experience, we are in agreement with Alexander that the intravenous injection of metrazol in 10 per cent solution is a good procedure to gauge the degree of depression. The first injection is usually 1 or 2 cc given quickly and if no response is elicited 3 to 4

cc are given a few minutes later Metrazol will exert a brief but powerful stimulation of the respiration in patients depressed by barbiturates and the degree or absence of the response is a rough measure of the profoundness of the depression This procedure is also of some differential diagnostic value Heinrich has found that 2 to 3 cc of metrazol will cause simulation of some degree in coma due to endogenous causes or carbon monoxide poisoning Absence of such an effect from this dose or from 3 to 5 cc of metrazol is supportive evidence of deep barbiturate depression

The first measures to be taken in all cases

cleared by suction using a soft rubber catheter, at half an hour or hourly intervals as needed We have found the administration of atropine sulfate in doses of $\frac{1}{160}$ to $\frac{1}{80}$ grain (0.4 to 0.6 mg) repeated as needed, to be useful in reducing excessive secretion An airway should be inserted to prevent the tongue from falling back and interfering with respiration Oral hygiene will help to reduce damage and infection of the mucous membranes of mouth and throat Oxygen administration is imperative in all cases of severe and prolonged barbiturate poisoning and is usually best accomplished by proper insertion of a nasal catheter which must be frequently removed and cleaned This is continued until all danger of hypoxia is definitely eliminated In some cases the help of a skilled anesthetist or bronchoscopist may become indispensable to prevent pulmonary atelectasis and to perform endotracheal intubation We have found it advantageous to raise the foot of the bed slightly, especially in patients in whom the gag and swallowing reflex is absent, aspiration of mucus is a frequent cause of dangerous and sometimes fatal bronchial infections or even pulmonary abscesses The patient should be frequently turned from one side to the other to prevent, as far as possible hypostatic congestion of the lungs

After these measures have been taken the appearance of many patients will be greatly improved, the depressed blood pressure will rise again the rales will disappear, and normal color will return In others, however,

improvement will be only slight and it is our opinion that further benefit can be obtained by vigorous antidotal treatment with stimulant drugs

The danger of prolonged deep depression in any patient is obvious and is the result of multiple factors, among which poor respiratory movements muscular atonia with pooling of blood and the possibility of aspiration

these factors Its primary aim must not be to awaken the patient as quickly as possible, but to restore normal reflex activity and improve respiration muscle tone, and circulation While many stimulants such as strychnine, caffeine and nikethamide (coramine) are of benefit in producing some stimulating effect in moderate depression the best available experimental and clinical evidence points to picrotoxin as the most powerful and useful antidote in severe barbiturate poisoning This nonalkaloidal drug, which has an exquisite antagonistic effect on the central nervous system against barbiturates has been introduced into the treatment of this condition on the basis of the work done by Maloney, Fitch and Tatum Its efficacy has been endorsed by numerous investigators who have extensive experiences with its use This fact is by now established far beyond the rather conservative evaluation which was made by the Council of Pharmacy and Chemistry of the A M A in 1939 Pentamethylenetetrazol (metrazol) can probably be considered the second drug in order of potency and is quite useful under certain circumstances as will be discussed shortly In contrast to the above named, such drugs as amphetamine (benzedrine) and desoxyephedrine (desodyn, methedrine) possess not only a central stimulating effect but also influence the circulation directly by their sympathomimetic stimulating action Their usefulness in severe barbiturate poisoning appears promising but is not yet as fully established as that of the other two drugs This subject has been reviewed re-

Picrotoxin is indicated only in severe cases of barbiturate poisoning and the hospital

should have a supply on hand sufficient to conduct vigorous treatment. If a patient is in deep coma with negative reflexes and absence of pain responses picrotoxin should be administered intravenously after the above described measures for adequate oxygenation etc. have been carried out. It is most convenient to inject the drug into the tubing of an intravenous drip infusion. The first dose should be 2 to 4 cc of a 0.3 per cent picrotoxin solution. The response of the patient should be watched during the next 15 minutes. The physician must never forget that picrotoxin even by intravenous administration has a latent period and a prolonged effect. The first positive action may consist of a slight and perhaps only transitory improvement of respiration or return of the corneal or pupillary reflex. If such response is absent or only fleeting another dose is injected 15 minutes later. Under most careful supervision this procedure is continued and the single doses may be raised to 5 or 6 cc. Stimulation is thus cautiously continued until the gag reflex returns, the respiration improves and the patient responds to painful stimuli or makes spontaneous movements. It is most important to watch for signs of over stimulation as evidenced by slight twitching of the facial muscles or of the extremities. Attempts to arouse the patient by the continuation of large doses of picrotoxin will almost certainly lead to generalized convulsions. A short transitory convulsive attack lasts usually only one minute but if such attacks are prolonged or repeated they should be treated by the intravenous injection of a small dose of a barbiturate such as pentothal sodium or with intravenous trimethadione (tridione). All physicians especially those not thoroughly familiar with picrotoxin should have such an antidote on hand. An attack of convulsions is invariably followed by a state of increased depression and naturally no analeptics of this type should be given for a while. An alternative method of administration consists of the continuous infusion of picrotoxin at the rate of 1 mg per minute. While good results have also been obtained with this procedure we favor the intermittent technique which we believe provides a greater safeguard against accidental overdosage. If the desirable state of increased

reflex activity has been attained or slight twitching has followed the last dose of the picrotoxin the amount of the single doses is decreased and the interval between injections is lengthened. The aim is now to keep the patient from relapsing into deeper coma and to proceed slowly and carefully with further denarcotization. In many instances it will be possible gradually to substitute intramuscular for intravenous picrotoxin administration.

While in a normal person 20 mg of picrotoxin may lead to serious toxic symptoms the presence of large amounts of barbiturates in the body results in a vast increase of tolerance to this analeptic drug. We have given as much as 5 gm over a period of about 10 days and Newman and Feldman have recently reported the use of more than 14 gm. Obviously this does not necessarily mean that these patients could not be saved with less and the object of the physician should be to give only as much picrotoxin as will produce the desired effect. However the absence of a toxic action of large doses on the function of other organs as we have frequently ascertained makes it possible to be governed entirely by the degree of the central stimulating effect of picrotoxin during its administration in barbiturate poisoning. In patients reacting favorably it still may be necessary to continue treatment around the clock for several days until consciousness is restored. On the other hand we have never seen recovery in any patient who failed to show at least some response after several hours of intensive therapy with this stimulant and other supportive therapy. Animal experiments by Richards et al have shown that intracisternal injection of picrotoxin is more powerful than the intravenous route and we believe that in desperate cases this procedure may become justified.

Metrazol has been used successfully as the sole analeptic drug in cases of severe barbiturate poisoning. Androp has described such a case where repeated injections of a 10 per cent solution were given at 15 to 30 minute intervals. The single doses varied from 5 to 11 cc. In our opinion picrotoxin is the preferable drug for the sustained treatment of severe poisoning because of its experimentally proved more powerful analeptic effect and its clinically longer dura-

tion Nevertheless we feel that metrazol has definite indications as follows as an immediate acting respiratory stimulant in the beginning of treatment when respiration is severely depressed or during acute respiratory embarrassment occurring later on in the course of such conditions Obviously artificial respiration is always the first thing to apply Furthermore we have successfully used metrazol injections during the treatment with picrotoxin in order to gauge the depth of depression The procedure is in general the same as that suggested by Alexander, to which we have referred above Incidentally we have found that in the absence of cyanosis the response to a few whiffs of 5 per cent carbon dioxide is also a good indicator of responsiveness of the patient Finally, metrazol is especially valuable in the later stages of a successful treatment where the patient has responded to picrotoxin, is restless but still depressed and will react with signs of overstimulation to increased picrotoxin doses The judicious use of metrazol injected intravenously in doses of 2 to 4 cc will frequently result in further denarcotization Metrazol appears to have a better cortical effect than picrotoxin and we

Recently sympathomimetic amines, especially amphetamine and desoxyephedrine have been recommended for the management of barbiturate poisoning (Freireich and Landsberg) These drugs are not only analeptics but also vasodepressors We believe that they may play a useful role in the treatment of barbiturate poisoning but that they should not be relied on as the sole agents in severe cases They can be successfully employed together with picrotoxin and other stimulants Single doses have ranged from 10 to 20 mg intravenously and such injections can be repeated at hourly intervals Under special circumstances, as much as 40 mg of amphetamine in single doses can be used under careful control of the circulation Because the vasodepressor action of these drugs may exhaust itself with too frequent injections of high doses, the blood pressure response should be checked repeatedly In our opinion special care should be taken to avoid unfavorable circulatory

effects in older persons or those suffering from cardiovascular disease These drugs, as ephedrine, are recommended for all patients, in whom the blood pressure fails to rise to normal levels or decreases unduly during the previously described management Neosynephrin (100 to 200 mg per liter) may be administered by intravenous drip to patients suffering from severe vascular collapse

A new idea for the treatment of barbiturate poisoning was introduced by Taubenhau and Soskin Since it is known that barbiturates do not interfere with the oxidation of succinate by brain slices in vitro, they suggested the administration of large doses of sodium succinate in barbiturate poisoning At present the practical usefulness of this procedure is controversial In our own experience and in that of many others with whom we have discussed this procedure no convincing effect on the course of this condition was obvious However, Barrett feels that this material exerts a definite respiratory stimulating effect and lightens barbiturate depression He suggests the intravenous use of a 30 per cent sterile solution of disodium succinate hexahydrate in distilled water, which is equivalent to an 18 per cent solution of sodium succinate Such a solution has been made available under the name of soduxin by Brewer and Company of Worcester Mass Barrett advises the immediate intravenous injection of 3 to 4 cc at the rate of 1 cc per second, this is usually followed by coughing Fifteen to 30 gm of the hydrated salt were administered within 15 minutes to adult patients As an alternative method, a 10 per cent solution may be given as intravenous drip infusion over 1 or 3 hours after an initial injection of a few cubic centimeters of the concentrated material If a physician decides to make use of this procedure, he must remember that large doses of sodium are thus given to the patient possibly resulting in an increased tendency for water retention and alkalosis Therefore, proper care must be taken to avoid undue changes in electrolyte balance

In addition to the above mentioned procedures, supportive treatment is of greatest importance Since the patient is comatose, perfect nursing care is mandatory This in-

cludes the prevention of burns by hot-water bottles, etc., catheterization, and the judicious use of intravenous fluids. This should be adjusted to produce about 1000 to 1200 cc of urine per day and is best obtained by the administration of dextrose and saline, however, not more than 1 liter of the latter is usually required. The tendency to pulmonary edema in severe cases requires prevention of overhydration and the same applies even more so if the suspicion of cerebral edema arises. For the first named condition we have sometimes successfully used the subcutaneous injection of pituitary extract preceded by 0.25 to 0.4 mg strophanthin-k or an equivalent amount of ouabain (strophanthin-g) intravenously. Cerebral edema is usually a bad prognostic sign, but an attempt can be made to influence it by intravenous injection of 50 cc of hypertonic sucrose or sorbitol solutions or the release of spinal fluid if the pressure is increased. Fever occurs almost always on the second or third day after the onset of the depression, prophylactic and therapeutic administration of antibiotics is important and the sulfa drugs may be used in therapeutic doses if indicated. Parenteral administration of vitamin B complex, and especially vitamin C in doses of 100 to 200 mg daily, is always indicated. Oral administration of liquid foods can be begun as soon as the swallowing reflex is definitely reestablished. With the return of consciousness special care on the part of the physicians and nursing personnel is indicated, particularly in patients who had taken the drug with suicidal intent. Psychiatric consultation and supervision of the patient to prevent him from repeating his attempt are strongly suggested.

RICHARD K. RICHARDS

REFERENCES

- Alexander, F. A. D. Amphetamine Sulfate for Acute Barbiturate Poisoning. *JAMA*, 131 1170, 1946.
- Androp, S. Use of Metrazol in Barbiturate Poisoning. Case Report. *Psychiatric Quart.*, 18 13, 1944.
- Barrett, R. H. Sodium Succinate—Clinical Use in Respiratory Depression. *Anesth. & Analg.*, 27 326, 1948.
- Barrett, R. H. Sodium Succinate: An Analeptic for Barbiturate Poisoning in Man. *Ann. Int. Med.*, 31 739, 1949.
- Burdick, D. L., and Rovenstine, E. A. Picrotoxin in Barbiturate Poisoning. *Ann. Int. Med.*, 22 819, 1945.
- Council on Pharmacy and Chemistry. Present Status of Picrotoxin in Poisoning by Barbiturates. *JAMA*, 112 431, 1939.
- Dresdale, D. T., et al. Barbiturate Poisoning Combined Use of Respirator, Fluid, Central Nervous System Stimulants and Pressor Agents. *Ann. Int. Med.*, 28 676, 1948.
- Eckenhoff, J. E., et al. Status Report on Analeptics. *JAMA*, 139 780, 1949.
- Fantus, B. Therapy of Cook County Hospital. Therapy of Barbiturate Poisoning. *JAMA*, 115 527, 1940.
- Freireich, A. W., and Landsberg, J. W. Amphetamine (Benzedrine) Sulfate for Acute Barbiturate Poisoning. *JAMA*, 131 661, 1946.
- von Heunich, A. Cardiazol zur Differentialdiagnose komatoöser Zustände. *Min. Wchnschr.*, 21 1106, 1942.
- Kornblau, A., and Resnick, S. Picrotoxin and Amphetamine (Benzedrine) in Barbiturate Poisoning. *Anesth. & Analg.*, 27 116, 1948.
- Maloney, A. H., and Tatum, A. L. Picrotoxin as Antidote in Acute Poisoning by Longer Acting Barbiturates. *J. Pharmacol. & Exper. Therap.*, 44 337, 1932.
- Maloney, A. H., Fitch, R. H., and Tatum, A. L. Picrotoxin as Antidote in Acute Poisoning by Shorter Acting Barbiturates. *J. Pharmacol. & Exper. Therap.*, 41 485, 1931.
- Metropolitan Life Insurance Company. Barbiturates Leading Cause of Fatal Accidental Poisoning. *Statistical Bull.*, 29 7, 1948.
- Newman, E. A., and Feldman, M., Jr. Massive Picrotoxin Therapy in Treatment of Acute Barbiturate Poisoning. *Arch. Int. Med.*, 81 690, 1949.
- Poe, M. F., and Karp, M. Phenobarbital Poisoning. Report of Case Treated with Massive Doses of Analeptics. *Anesth. & Analg.*, 27 176, 1948.
- Richards, R. K., and Menaker, J. G. Role of Picrotoxin in Treatment of Acute Barbiturate Poisoning. *Anesthesiology*, 3 37, 1942.
- Richards, R. K., Grimes, C., and Smith, A. Intracerebral Administration of Picrotoxin. *Am. J. Physiol.*, 133 423, 1941.
- Soskin, S., and Taubenhaus, M. Sodium Succinate. *Ann. Int. Med.*, 22 819, 1945.

Therap., 10 43, 1943

BROMIDE INTOXICATION

With few exceptions bromide intoxications are the result of prolonged therapeutic administration of high or occasionally even moderate doses of inorganic bromide preparations. Such incidences have been reported after daily consumption of 40 to 50 grains of alkali bromides for 14 weeks, or after shorter periods with higher doses.

Fatal outcomes are rare but have occurred with blood bromide levels of 325 mg per 100 cc

The symptoms consist chiefly of depression on ataxia incoordination of speech hallucinations and frequently paranoid ideas. Toxic delirium is most liable to develop in persons suffering from a psychoneurosis (Millikan and Paul). Such findings should warn the physician to have a blood bromide determination made even if the patient or members of the family deny bromide medication as many nostrums contain this chemical in a disguised form. The so called bromide acne in its various manifestations is quite often absent even in severe cases of chronic bromide poisoning its occurrence is independent of the blood bromide concentration. The bromide level in the blood is normally below 25 mg per 100 cc blood. The level at which toxic symptoms appear varies considerably persons in a poor nutritional state in advanced age or suffering from renal dysfunction may show intoxication with 75 mg per 100 cc (Angyal) while on the other hand epileptics may show hardly any depression with 100 to 125 mg per 100 cc blood. Usually values above 150 mg per 100 cc are definitely indicative of bromide intoxication. Alcoholics are also more liable to develop intoxication after in-

with marked restlessness which is sometimes accompanied by increased cerebrospinal pressure a therapeutic spinal tap is indicated and other sedatives such as paraldehyde or phenobarbital are necessary (Gundry). Adequate nutrition must be provided. In severe cases sodium chloride may have to be administered intravenously as a 2.5 per cent solution. This should be followed by oral administration in doses of 6 to 12 gm daily in divided doses. A part may be given in the form of salted foods and the balance in capsules with a sufficient amount of water. Some authors claim favorable results by combining this treatment with intramuscular injections of 5 cc of adrenal cortical extract for the first few days. It is desirable to follow the blood bromide and blood chloride levels during this treatment. Care should be taken not to overload older persons particularly those with circulatory and renal impairment with large amounts of sodium chloride and fluids. In such patients a more gradual replacement therapy appears logical. Under

on and some clinical similarity of the symptomatology of bromide intoxication and pellagra it has been recently recommended that the conventional sodium chloride therapy be supplemented with daily doses of 600 to 750 mg of nicotinamide. Clinical evidence so far is meager but this approach may be well worth further consideration.

RICHARD A. RICHARDS

mg of sodium bromide are equal to 116 mg of bromide ion (Detweiler).

Bromides are rapidly absorbed and tend to replace chlorides in the body thus even the gastric juice may contain hydrobromic acid. If about 25 to 30 per cent of the body chloride is replaced by bromide definite symptoms are present and fatalities occur above 40 per cent. For practical purposes the excretion of chlorides and bromides by the kidneys takes place in proportion to their relative concentration in the blood from this it follows that only small amounts of bromides will leave the body during the first weeks of treatment until considerable amounts have been accumulated.

The treatment is directed to reverse the accumulation of bromides by withdrawal of this medication and administration of large amounts of sodium chloride. In severe cases

REFERENCES

- Angyal A. Predisposing Factors in Bromide Intoxication. *Arch. Neurol. & Psychiat.* 49:359 1943.
- Bondurant C. P. and Campbell C. Adrenal Cortex Extract in Treatment of Bromide Eruption and Bromide Intoxication. *J. A. M. A.* 116:100 1941.
- Detweiler H. K. Bromide Intoxication. *Canad. M. J.* 48:309 1943.
- Gundry L. P. Bromide Intoxication. *J. A. M. A.* 113:466 1939.
- Harris R. S. and Derman P. M. Nicotinamide in Bromide Intoxication. *South. M. J.* 42:973 1949.
- Kitching H. H. Mental Symptoms in Bromide Intoxication. *Brit. M. J.* 1:54 1942.
- Millikan C. H. and Paul W. D. Results of Administration of Varying Doses of Sodium Bromide. *J. Iowa M. Soc.* 36:39 1946.

ARSENIC POISONING

The toxicologic importance of arsenic is given by the various forms in which it may lead to poisonings. These may be accidental, criminal, suicidal, medicinal, or occupational. Arsenous oxide, Fowler's solution, and the gas arsine are the most important inorganic compounds of the organic forms. The various arsenicals used in chemotherapy are of special interest. Arsenic-containing insecticides, certain dyes, and paints, and various industrial uses may lead to accidental or occupational poisoning. Arsenic in various forms can cause acute or chronic intoxication.

Acute Poisoning. While intoxication with inorganic arsenicals may occur by absorption from the skin, the most frequent route is the digestive tract, followed by inhalation of dust or the gaseous arsine, or by injection of

tally used for the gastric lavage and later administered in teaspoonful doses with milk. This mixture has at least some absorbent effect and will thus retard absorption of the arsenic. Activated charcoal can be used instead. A laxative dose of magnesium sulfate or castor oil should be given to hasten the elimination through the bowel. The symptoms following vascular collapse require energetic treatment by the administration of vasoconstrictors, e.g., epinephrine or related compounds, as well as a central stimulant such as nikethamide (coramine) or metrazol. It appears reasonable to prevent dehydration by intravenous fluid administration, and one would expect plasma or gelatin infusions to be of value. The mortality from acute arsenic poisoning in the pre-BAL era ranged from 50 to 75 per cent. Death has followed the ingestion of as little as 60 mg. arsenous trioxide. 0.1 to 0.3 gm. were usually fatal, but larger doses have not always been fatal.

Pharmacologic Properties of BAL and Its Use in the Therapy of Arsenic Poisonings. It has been known for some 20 years that the toxicity of many heavy metals and arsenic is at least partially due to their combination with the sulfhydryl groups of the enzyme proteins. Voegtlin et al. showed in 1923 that certain substances containing sulfhydryl groups could counteract the toxic action both in vitro and in vivo. British investigators, who were seeking antidotes against the arsenic-containing war gas lewisite, developed several compounds of this nature and found that the dithiols are even more effective than the monothiols (Peters et al., Stocken and Thompson). The chemical deemed most suitable was 2,3-dimercaptopropanol, briefly called BAL, an abbreviation of British anti-lewisite.

Extensive biochemical and pharmacologic studies with this material, carried out in England and in the United States, have shown that BAL not only neutralizes arsenic and certain heavy metals in vivo by preventing the attachment of the poison with vital cell enzymes, but within limits can even revert such combination after it has occurred.

Aqueous solutions of BAL are unstable, and a 10 per cent solution in peanut oil containing 20 per cent benzyl benzoate (Hynson, Westcott, and Dunning) is now almost

that the most dramatic action of inorganic arsenicals is their profound paralyzing effect on the capillaries, especially those of the intestinal tract. Thus violent diarrhea, followed by dehydration and general vascular collapse, are the predominant features. Usually a few hours elapse before symptoms appear after ingestion, but with overwhelming doses, coma, unconsciousness, and death can follow quickly after the intake of the poison without gastro-intestinal symptoms.

The treatment should be directed to the removal of unabsorbed poison by washing the stomach repeatedly. Arsenous oxide tends to cling to the folds of the gastric mucosa, making its removal difficult. The treatment of poisoning with arsenicals has been radically changed by the discovery of BAL, which will be discussed in detail later.

stomach has been evacuated, one may administer a freshly prepared ferric hydroxide suspension. This is done by diluting 15 cc (½ oz.) of tincture of ferric chloride with

universally used for intramuscular injection BAL is by no means nontoxic. In animals toxic doses produce lacrimation, muscular inco-ordination finally generalized convulsions and death. There are no typical anatomic findings. Side effects even with therapeutic doses in man are not uncommon and are noted in about 15 per cent of the cases with doses of 4 mg per kilogram of body weight and in more than 50 per cent at 5 mg per kilogram. Aside from moderate pain at the site of injection and the rare occurrence of sterile abscesses, mild systemic effects consist of lacrimation, salivation, a burning feeling in the mouth and eyes, anxiety, and a moderate rise of blood pressure. These symptoms disappear usually within 1 to 1½ hours after intramuscular injection, only exceptionally lasting longer than 4 hours. Woody and Kometani observed a child who by mistake received two doses of 8 mg per kilogram of BAL each at 3 hour intervals. Symptoms as described above disappeared within an hour after the first injection; they were more severe after the second and an attack of convulsions followed by depression occurred, but the child recovered completely without sequelae. BAL is also absorbed through the skin, as has been proved both experimentally in animals and clinically in humans. However, it is somewhat irritating, causing local erythema, whealing and itching. If the skin had been damaged previously by mustard gas dermatitis occurred in 66 per cent after local application. Nine per cent of the patients who were treated with the 5 per cent BAL ointment developed various forms of skin reactions of an allergic nature. Cutaneous sensitivity can also be produced by intramuscular injections. It is agreed by most investigators that BAL administration increases the output of arsenic in the urine. This follows both

with arsenites such as Fowler's solution may develop toxic side effects. However, this should not deter one from the use of BAL in cases of serious poisoning with such preparations.

Clinically BAL has been used successfully in various forms of arsenic poisoning. Woody and Kometani used it in 42 children, half of whom had probably taken lethal amounts of arsenic containing substances. There were no fatalities in this series and the symptoms of poisonings were under control within 12 hours after institution of the BAL therapy. The drug was likewise successfully applied in 2 patients who by error had received 400 and 600 mg of mapharsen, while another died after 1200 mg, probably because therapy was discontinued too early (Eagle and Magnusen). Other successful uses include arsenic encephalitis, blood dyscrasias following arsenical therapy, optic complications, and exfoliative dermatitis caused by injection of arsenicals. In the latter condition the duration of severe symptoms was cut about in half with a particularly favorable effect on the oozing form of toxic dermatitis.

The Council on Pharmacy and Chemistry of the A.M.A. has suggested the following treatment schedules for the use of intramuscular BAL injections in severe arsenical poisonings, especially the encephalitic type, exfoliative dermatitis, overdosage of arsenicals or blood dyscrasias. A dose of 3 mg of BAL per kilogram in oil should be injected six times a day at intervals of 4 hours. On the third day four injections are recommended and for the following 10 days two daily injections or until recovery occurs. In milder cases only four daily injections of 2.5 mg per kilogram each for the first 2 days followed by two injections on the third day and one daily injection for the next 10 days. In serious cases it may be desirable to exceed these recommendations for the first two doses as it has been found that four doses of 5 mg per kilogram each can be given at 4 hour intervals without serious acute or cumulative toxic effects. Administration of 25 mg ephedrine sulfate by mouth half an hour prior to the injection of BAL reduces the toxic side effects (Tye and Siegel). Administration of BAL ointment (5 per cent) to the skin in exfoliative arsenical dermatitis or of a suitable ointment of aqueous

ated and it is still not fully explained why animals receiving nonfatal doses of sodium arsenite together with BAL developed severe stimulation of the central nervous system which does not occur with either of the two compounds alone (Koppanyi and Sperling). Thus it is theoretically possible that the use of BAL in cases of poisoning

solution to the eye in case of lewisite burns has been investigated but the clinical experience is still limited and such preparations are not commonly available. Theunction of BAL ointments in these cases is painful and this factor, as well as the possibility of sensitization, seems to militate against the routine use of this therapy. Eagle is undecided about the usefulness of BAL in jaundice occurring during treatment with arsenicals, results were good in about half of the cases. The causative role of arsenic in this condition has been questioned by others. It should be used with care in patients with impaired liver function (Cameron et al.).

BAL is apparently not effective in preventing the dangerous hemolytic reaction following poisoning by arsine. The ethyl ether derivative of BAL shows an antagonistic effect in animals but its great toxicity seems to preclude its use in humans. There is no definite evidence in one way or another whether or not BAL will favorably affect late toxic effects of arsine. Management of arsine poisoning is still unsatisfactory. Oxygen should be administered together with other symptomatic treatment. Repeated blood transfusions may become necessary and the patient should be protected as far as possible against the consequences of the hemolytic action of this poison. This should include ample fluid administration to prevent anuria and proper treatment of this condition if it should develop. Peritoneal lavage may be useful to prevent fatal azotemia.

For prevention and management of the various forms of acute side effects during treatment with arsenicals, such as nitritoid reactions and therapeutic shock, the reader is referred to textbooks on syphilology.

Chronic Poisoning. With the decrease of the use of arsenic in therapeutics as well as in industry, the incidence of chronic poisoning appears to be on the decline. The diagnosis of chronic arsenic intoxication can be difficult because of the various manifestations which resemble frequently endogenous conditions such as gastrointestinal disturbances, chronic bronchitis, skin disorders, polyneuritis and degenerative changes of the parenchymatous organs. The treatment is based on elimination of the cause and general supportive and symptomatic treat-

ment. Daily intravenous injections of 0.5 gm. of sodium thiosulfate may be tried. The possible effect of BAL remains to be established.

RICHARD K. RICHARDS

REFERENCES

- Cameron, G. R., Burgess, F., and Trenwith, V. S. Possibility of Toxic Effects from 2, 3 Dimercaptopropanol in Conditions of Impaired Renal or Hepatic Function. *Brit J Pharmacol*, 2: 59, 1947.
- Council on Pharmacy and Chemistry. "BAL" (British Anti Lewisite) in the Treatment of Arsenic and Mercury Poisoning. *JAMA*, 131: 824, 1946.
- Eagle, H. The Systemic Treatment of Arsenic Poisoning with BAL (2, 3 Dimercaptopropanol). *J Ven Dis Inform*, 27: 114, 1946.
- Eagle, H., and Magnuson, H. J. Systemic Treatment of 227 Cases of Arsenic Poisoning (Encyclopedia of Dermatology, 1947).
- Fewe, J. Sy.
- Koppa. nomic Effects Following Combined Administration of Sodium Arsenite and 2, 3 Dimercaptopropanol (BAL). *J Pharmacol & Exper Therap*, 89: 350, 1947.
- Mann, P. J. G., and Quastel, J. H. Toxic Effects of Oxygen and of Hydrogen Peroxide on Brain Metabolism. *Biochem J*, 40: 133, 1946.
- Peters, R. A., Stocken, L. A., and Thompson, R. H. S. British Anti Lewisite (BAL). *Nature, London*, 156: 616, 1945.
- Randall, R. V., and Seeler, A. O. BAL. *New England J Med*, 239: 1004, 1948.
- Salaman, M. H., et al. Prevention of Jaundice Resulting from Antisyphilitic Treatment. *Lancet*, 2: 7, 1944.
- Stocken, L. A., and Thompson, R. H. S. British Anti Lewisite, Dithiol Compounds as Antidotes for Arsenic. *Biochem J*, 40: 535, 1946.
- Stokes, J. H. *Modern Clinical Syphilology, Diagnosis, Treatment, Case Study*. Philadelphia: W. B. Saunders Company, 1944.
- Sulzberger, M. B., Baer, H. L., and Kanof, A. Clinical Uses of BAL. *J Clin Investigation*, 25: 474, 438, 1946.
- Symposium. Toxicity of BAL. *J Pharmacol & Exper Therap*, (Suppl.), 87: 23, 28, 33, 41, 60, 1946.
- Tye, M., and Siegel, J. M. Prevention of Reaction to BAL. *JAMA*, 134: 1477, 1947.
- Voegtlin, C., Dyer, H., and Leonard, C. S. Mechanism of Action of Arsenic upon Protozoa. *Pub Health Rep*, 39: 1882, 1923.
- Waters, L. L., and Stock, C. BAL (British Anti Lewisite). *Science*, 102: 601, 1945.

MERCURY POISONING

Of accidental or suicidal poisonings with mercury, the ones following the ingestion of soluble mercury salts, especially bichloride

of mercury are the most important. Fortunately this compound leads to prompt vomiting in many instances thus reducing somewhat the danger of serious poisoning. Nevertheless such intoxication must always be considered serious especially so because of the quick absorption of these salts from the mucous membranes. If vomiting does not occur promptly the prognosis is serious with 10 gm or more of bichloride of mercury. This applies equally to other soluble salts. Whether or not vomiting has occurred the stomach must be evacuated immediately by gastric lavage or induction of vomiting followed by lavage. The washing fluid should contain about 1 teaspoonful of sodium bicarbonate per pint. Sodium chloride solutions by mouth are to be avoided because they favor the solubility of bichloride of mercury. Administration of skimmed milk (fat increases absorption) or the white of several eggs has been recommended and there is some experimental evidence that charcoal binds mercury salts. It must be kept in mind that these procedures are based on a temporary absorption of the poison which will not prevent its ultimate absorption. Thus quick elimination by stomach washing or less reliably by administration of a saline laxative must supplement such temporary expedients.

As in arsenic poisoning the treatment of mercury poisoning has been revolutionized by the introduction of BAL. The basic principles have been discussed under arsenic poisoning and likewise arsenic treatment should be early and vigorous. Somewhat higher initial doses than those routinely used in arsenic poisoning are recommended in the treatment of intoxication with mercury salts. The first injection should consist of 5

about 4 hours. In severe cases another such dose is given within the first 12 hours after start of the treatment. On the second day two doses of 2.5 mg per kilogram are administered and on the third day one dose. Further continuation will depend on individual circumstances. A slightly different scheme has been recommended by Batson and Peterson who use 3.5 to 4.5 mg per kilogram as the initial dose followed in 2 hours by 2 to 3 mg

Longcope and Luetscher did not lose any of the 37 patients in whom BAL injections

supplemented by additional supportive measures.

If BAL is not immediately available an attempt should be made to use one of the following treatments until BAL administration can be instituted. Sodium formaldehyde sulfoxylate has been recommended by Rosenthal and by others (Wolpaw and Alpers). A freshly prepared 3 per cent solution is used for stomach lavage and 200 cc of it are given orally. This may be supplemented by slow injection (20 to 30 minutes) of 10 gm of pure salt in 200 cc of distilled water. This may be repeated 4 to 11 hours later. As a second choice sodium thiosulfate can be given orally in amounts of 1 to 2 gm and intravenously by injecting 20 cc of a 5 per cent solution. These procedures will probably affect only mercury which is not yet fixed in the tissue but they should be carried out promptly until systemic BAL treatment can be started.

In cases of severe poisoning it will be necessary to treat shock by the established methods including administration of blood plasma and intravenous crystalloid fluids. It is well known that mercury salts damage the kidney and also cause colitis because they are partially excreted through the intestine. For the latter repeated colonic flushing has been recommended using either a 1:1000 solution of sodium formaldehyde sulfoxylate or one of 0.5 gm of calcium sulfide per liter. The severe necrotizing nephrosis is the most dangerous consequence of mercury poisoning and may lead to death by anuria within a few days. Albuminuria with the appearance of casts and blood are the early signs of kidney involvement. Blood chlorides and NPN should be carefully watched and a consistent drop of the former and a rise of the latter are prognostically unfavorable signs.

The management of this condition is in general the same as that of anurias from other causes. Peritoneal lavage may be helpful in preventing fatal azotemia. This procedure has been used successfully by Batson and Peterson and their publication should be consulted for the composition of the washing solution and the technique of its administration. The question of the usefulness of kidney decapsulation has not been completely settled as yet but does not seem to be favored by recent investigators.

Recently a number of serious and sometimes fatal accidents have been reported following the intravenous injection of various mercurial diuretics. In some instances circulatory disturbances, collapse, fever or anaphylactoid reactions have occurred. Fatalities were usually due to cardiac effects, probably the occurrence of ventricular fibrillation, but respiratory failure or anaphylactic shock may have been responsible for a few. The change from one preparation to another eliminates the intolerance for some patients (Barker et al., DeGraff and Nadler). The treatment of the acute episode is entirely symptomatic. Intramuscular injection of these drugs is much safer and is advisable unless particular reasons require the intravenous route.

RICHARD K. RICHARDS

REFERENCES

- Barker M H, Lindberg H A and Thomas M E: Sudden Death and Mercurial Diuretics. *JAMA* 119:1001 1942.
- Batson R and Peterson J C: Acute Mercury Poisoning: Treatment with BAL and in Anuric States with Continuous Peritoneal Lavage. *Ann Int Med* 29:278 1948.
- Council on Pharmacy and Chemistry: BAL (British Anti-Lewisite) in the Treatment of Arsenic and Mercury Poisoning. *JAMA* 131:824 1946.
- DeGraff A C and Nadler J E: Review of Toxic Manifestations of Mercurial Diuretics in Man. *JAMA* 119:1006 1942.
- Longcope W T and Luetscher J A Jr: Clinical Uses of 2,3-Dimercaptopropanol (BAL): Treatment of Acute Mercury Poisoning by BAL. *J Clin Investigation* 25:557 1946.
- Rosenthal S M: Antidote for Acute Mercury Poisoning. Preliminary Report. *JAMA* 102:1273 1934.
- Wolpaw R and Alpers N: Treatment of Acute Mercury Poisoning with Sodium Formaldehyde Sulfocylate with Review of 20 Cases. *J Lab & Clin Med* 27:1387 1942.

LEAD POISONING

Lead may enter the human body accidentally usually due to occupational exposure (1) by inhalation of lead containing dust or fumes as metal salts or organic lead compounds (2) by ingestion (3) by absorption through the skin usually of tetraethyl lead, the well known "anti knock" fluid in gasoline. The first named route is today the most common cause in the United States. Occasionally other mechanisms such as absorption from embedded lead shot are involved. It should be remembered that exposure to lead does not necessarily mean lead poisoning. With the so-called normal diet the average person takes in small amounts of lead but absorption from the intestinal tract is poor and as long as the excretion keeps up with absorption poisoning does not occur. In contrast absorption from the respiratory tract is much more extensive.

Laboratory methods if conducted by experienced personnel and judged in connection with other factors are of great diagnostic help. Briefly the following values indicate a dangerous degree of exposure: basophil "stippling" in more than 800 to 1000 red cells per 1,000,000; a fecal lead content of more

per liter of whole blood indicates severe exposure and suggest poisoning at 10 mg per liter or higher (Kehoe et al.).

It is advisable that these determinations be made while the patient is still under exposure because the findings are subject to rapid change after removal from his usual occupational surroundings. Workers may have laboratory findings in the above mentioned order of magnitude without clinical symptoms but abnormal findings are a warning sign and are supportive evidence in the presence of clinical disease. On the other hand the absence of abnormal amounts of lead in the urine, blood and feces on repeated examination under suitable conditions are incompatible with the diagnosis of lead poisoning. The well known lead line in the gums can exist in exposed persons without evidence of sickness. Details of the clinical symptomatology and diagnosis of lead poisoning are not discussed here.

If the abdominal pain which is usually the outstanding symptom is severe hospitalization is advised. Intravenous calcium therapy should be instituted by injection of 10 cc of calcium gluconate or gluconogluconate (neocalglucon) or 5 cc of 10 per cent calcium chloride solution. Four to 10 minutes should be used for each injection; these must be repeated several times during the next few days until abdominal pain is under control. The first two preparations named can be given intramuscularly after the acute phase has been overcome. Wilentz recommends "around the clock" intravenous calcium therapy for the first period in all

cases tried to break the paroxysmal spasm. In rare instances the use of narcotics may become unavoidable and it appears reasonable to try first meperidine hydrochloride (demerol) in doses of 100 mg subcutaneously before resorting to morphine. Hot applications to the abdomen are usually well tolerated.

After the acute attack has been controlled the bowels should be emptied by giving 1/2 to 1 oz of magnesium sulfate and a mild laxative is recommended during the following days to combat constipation. In most cases it will be possible to control the colic in 1 or 2 days. Parenteral calcium therapy is gradually substituted by oral administration as 1 gm calcium gluconate four times daily. The diet should contain ample milk, calcium and phosphorus for the next several weeks. Formation of kidney stones under this treatment has been seen occasionally (Cotter). Iron preparations are indicated only in the second period of the treatment in order to combat anemia. Naturally all possibilities of exposure to lead should be excluded and outdoor exercise and a nutritious diet with the addition of vitamins will help to overcome weakness and malaise.

The intestinal symptoms disappear at the latest within 2 to 4 months without leaving permanent sequelae but neuritic complications can persist for a considerably longer period.

It has been assumed for some time that

lead and calcium follow an essentially similar metabolic behavior in the body (Aug). Accordingly procedures favoring calcium retention will also tend to deposit lead especially in the bones which are by far the most important storage place during prolonged exposure to this metal. Conversely mobilization of calcium will result in "deleading" with increased urinary lead excretion. During the acute phase the therapy as we have discussed it is directed to removing the lead from the circulation and favors its immobilization in the skeleton.

The long favored procedure of "deleading" the patient after the acute symptoms have completely subsided (never before) has recently lost ground. Consequently we shall discuss this form of treatment only briefly. In general it is based on bringing the patient into negative calcium balance which is thought to release lead from the tissues into the blood stream followed by increased excretion through the kidneys. For this purpose the patient is placed on a low calcium diet avoiding all milk, milk products and green vegetables, while meat and colored vegetables, butter and fat are permitted. Three to 4 days later ammonium chloride is added with an initial dose of 1 gm three times daily. This is given as a solution with ample water during the meals or in the form of enteric coated tablets to avoid gastric irritation. If tolerated the ammonium chloride intake can be gradually stepped up to 8 gm daily. The patient may have some nausea, loss of appetite and weight but these symptoms disappear on withdrawal or reduction of the medication. Strict medical supervision is necessary and the occurrence of acute attacks of lead colic under this treatment necessitates its discontinuance. A 2 or 4 week employment of this regimen is recommended. Other schemes use potassium iodide (0.5 to 2.5 gm per day), sodium bicarbonate (20 to 40 gm daily) or other agents with the idea of lead mobilization. After the patient has finished one course of deleading, he is placed on a high calcium diet to replenish his calcium stores and the whole procedure may be repeated for a few times at intervals (Hunter).

One of the recent innovations is the use of 2,3-dimercaptopropanol (BAL). This sub

stance is known to possess a great affinity to certain metals and its detoxifying properties are discussed in connection with its use in mercury and arsenic poisoning. Telfer has used BAL in lead poisoning giving it in doses of 19 mg per kilogram for 5 days or even longer in some instances. Twelve such injections were given. This was followed 17 days later by four daily injections of 25 mg of BAL per kilogram for 19 doses. Kehoe in a recent study has reviewed this procedure and reported on the results obtained with the injection of 5 mg of BAL per kilogram. This resulted in a decrease of the blood lead content and a 34 fold increased lead output in the urine. Apparently BAL releases the lead from its combination with the red cells but no extensive deleading of the body appears to take place.

Recent investigators (Kehoe, Wilentz) agree that only insignificant amounts of lead are released from the body by any of the deleading procedures which in addition are potentially harmful. While the final decision on this whole subject has certainly not yet been reached the present tendency does not favor deleading with or without the use of BAL as a routine procedure in the management of chronic lead intoxication but it must still be considered permissible in individual cases.

Acute lead poisoning due to consumption of soluble lead salts is treated by gastric lavage followed by administration of a laxative dose of magnesium sulfate. Intravenous calcium therapy and other management should be instituted as outlined above. Sollmann states that 10 gm of soluble lead salts have caused death while as much as 30 gm have been survived. There is no present clinical experience of the possible effect of BAL on acute lead poisoning and animal experiments do not indicate that it is of value (Weatherall).

The severe acute encephalopathy which may follow especially after the inhalation of tetra ethyl lead can lead to toxic delirium and a variety of nervous and mental symptoms. Intravenous infusions of 2 to 4 gm magnesium sulfate in 2 per cent solution combined with oral doses of pentobarbital as indicated have been recommended (Machle). Other symptomatic treatment is instituted as required followed by the man-

agement of lead poisoning as described above.

RICHARD K. RICHARDS

REFERENCES

- Aug J C: Biochemical Behavior of Lead in Body. *JAMA* 104:87 1935
 Cantaro v A and Trumper M: *Lead Poisoning*. Baltimore: Williams & Wilkins 1944
 Cotter L H: Lead Intoxication by Inhalation. *J Indust Hyg & Toxicol* 23:44 1946
 Hunter D: *Industrial Toxicology* (Croonian Lectures 1942). London: Oxford Clarendon Press 1944
 Kehoe R A: Personal communication
 Kehoe R A et al: *Occupational Lead Exposure and Lead Poisoning*. New York: American Public Health Association 1943
 Machle W F: Tetra ethyl Lead Intoxication and Poisoning by Related Compounds of Lead. *JAMA* 105:578 1935
 Ryder H W, Cholak J and Kehoe R A: Influence of Diethylopropanol (BAL) on Human Lead Metabolism. *Science* 105:63 1947
 Sollmann T: *Application of Poisons*. Philadelphia: J. C. Lippincott 1947
 Weatherall M: Effects of BAL and BAL Glucoside in Acute Lead Acetate Poisoning. *Brit J Pharmacol* 3:137 1948
 Wilentz W C: Treatment of Lead Intoxication. *JAMA* 139:823 1949

MANAGEMENT OF BITES BY DOMESTIC SNAKES

The venom of the North American snakes possesses various toxic components which affect the tissues locally by causing swelling, edema and gangrene as well as severe systemic effects on the respiratory center, nervous system, muscles, heart, blood and circulation. Mortality without specific treatment is estimated at about 11 per cent with it at about one fourth of this figure. Death may occur several hours or a few days after the bite. The generally accepted emergency treatment consists of the application of a tourniquet a few inches above the bite. The constriction should be strong enough to weaken but not to abolish completely the pulse peripheral to it. The tourniquet should be released for 3 minutes every half hour until antivenom can be administered. An antiseptic is applied to the bite and crosswise incisions $\frac{1}{2}$ in long and $\frac{1}{4}$ in deep

are made with a sharp knife avoiding possible injuries to underlying larger blood

should be rinsed repeatedly with a dilute solution of potassium permanganate which destroys the venom. Suction should be repeated for 15 to 20 minutes every hour. If swelling progresses the tourniquet has to be moved farther centrally and additional incisions can be made to which suction can also be applied. Applications with strong salt or epsom salt solutions are made to encourage drainage. The patients must be kept as quiet as possible and should not be allowed to walk. Small doses of analgesics or sedatives can be given to relieve pain and anxiety and copious intravenous infusions with saline or blood are suggested for severe cases. Contrary to popular belief the administration of alcohol is inadvisable. The use of stimulants is necessary in cases of collapse.

An effective specific antidote has been prepared under the name of antivenin by Wyeth Inc. of Philadelphia which is a polyvalent equine hyperimmune serum against rattlesnake, copperhead and moccasin venoms but not against that of the coral snake which is native to the southern United States. This serum is available in a dried form which is stable for at least 5 years. It may still be lifesaving in desperately sick patients. Large doses (75 cc) and repeated administration may be necessary. Because of its preparation from horse serum the patient must be tested for hypersensitivity and it may be wise to have an intravenously injectable antihistaminic and epinephrine available.

Detailed instructions regarding dosage, route of administration and precautions are contained in the directions which accompany each package of antivenin. The manufacturer has also prepared an instructive booklet on the treatment of snake bites on which we have drawn freely for this outline.

RICHARD K. RICHARDS

BLACK WIDOW SPIDER BITE

The black widow spider (*Latrodectus mactans*) occurs in the United States chiefly in the southern and the western coastal regions but occasionally in other parts of this

country and in Canada. The poison is of protein like nature and by weight is more toxic than that of the rattlesnake. Nevertheless fatalities seem to be exceedingly rare. The bite is followed within 15 minutes by violent pain over the whole body, nausea, and even delirium and convulsions. Marked abdominal rigidity may sometimes lead to confusion with intra abdominal emergencies. The blood pressure is usually elevated and the occurrence of a peculiar burning sensation of the soles of the feet 24 hours after the bite has been reported as a typical symptom (Frank).

The treatment is both specific and symptomatic. The former can be carried out by prompt injection of 1 to 2 units of *Latrodectus mactans antivenin* (Wyeth Inc. Philadelphia). Tests for sensitivity are made before the intramuscular injection of this antiserum and the precautions and instructions accompanying the package must be carefully observed. The preparation is available in a dried state and will keep for about 5 years. Usually it will take a few hours before this treatment becomes effective. In the meantime and if no antiserum is available prompt symptomatic treatment is obligatory. The results obtained with the various procedures are not uniform and the various investigators favor different methods. A brief résumé of the most frequently applied procedures follows.

Intravenous injection of 10 cc of a 10 per cent solution of calcium gluconate or calcium chloride is favored by many authors. This dose may have to be repeated several times within 2 to 4 hour intervals. Magnesium sulfate in a 6 to 10 per cent solution may be given by slow intravenous injection up to 20 cc per dose under careful observation (Ginsburg). It must be kept in mind that large amounts of magnesium may seriously depress respiration. Such accidents must be promptly counteracted by the physiologic antagonist of magnesium ions, namely, calcium salts given intravenously and the hypodermic injection of neostigmine methylsulfate (prostigmine) in doses of 0.5 mg. Artificial respiration may be instituted if necessary. Often morphine is indispensable to combat the severe pain. This can be administered in doses of $\frac{1}{4}$ to $\frac{1}{2}$ grain (15 to 30 mg.), subcutaneously or $\frac{1}{4}$ grain (7.5 mg.),

intravenously at a slow rate. In children a grain (30 mg) of codeine phosphate subcutaneously has been found satisfactory. Morphine and magnesium are synergistic in their depressant effect on the respiration and this should be kept in mind in directing the treatment.

A recent suggestion which is still in need of more extensive confirmation is the intramuscular injection of 2 cc of $\frac{1}{4000}$ neostigmine methylsulfate (prostigmine methylsulfate) with $\frac{1}{150}$ grain (0.4 mg) of atropine sulfate. This has been reported to have brought relief within 15 minutes and the dose can be repeated four times at 4 hour intervals (Bell and Boone Beck).

While the pain usually decreases without sequelae milder attacks may recur from 1 to 4 days after the bite. The average duration is 30 to 40 hours. The use of hot baths has been found beneficial in relieving temporarily the marked muscular pain. It should

be noted that in contrast to snake bite no local treatment such as suction or incision is advised. Simple cleansing and dressing are sufficient.

RICHARD K. RICHARDS

REFERENCES

- Beck E J. Neostigmine for Black Widow Spider Bite. Case. *J M A Georgia* 36:372 1947.
 Bell J E Jr and Boone J A. Neostigmine Methyl Sulfate an Apparent Specific for Arachnidism (Black Widow Spider Bite). *J A M A* 129:1016 1945.
 Frank L. Black Widow Spider Bite Syndrome. *M I Surgeon* 91:399 1949.
 Ginsburg H M. Black Widow Spider Bite. Report of 44 Cases. *California & West Med* 46:381 1937.
 Greer W E R. Arachnidism. Effect of Calcium Gluconate in 11 Cases. *New England J Med* 240:5 1949.
 Kirby South H T. Specific Treatment of Black Widow Spider Bite. *South M J* 38:696 1945.

DISEASES OF THE NERVOUS SYSTEM

A THERAPEUTIC APPROACH TO
PSYCHOSOMATIC PROBLEMS

The first thing to do if one is to treat psychosomatic problems successfully is to make the correct diagnosis. Naturally one does not help a patient with let us say hysterical bloating if one operates for a supposed intestinal obstruction.

The Need for a Good History Essential in the treatment of persons with nervous diseases is the taking of a good history, and especially a history which causes the patient to see how he or she got into difficulties. Occasionally, after the physician has taken

now that it is all up to me and I'll go home and do what I have to do to straighten things out."

Another way in which a physician almost cures a nervous patient as he takes a good history is by showing that he knows the disease well. A badly worried person is cheered and encouraged when he sees that his disease is not so rare and inexplicable as he thought it was. It was the unknown that was frightening him.

Often all the physician has to do to help a woman with a so called mucous colitis is to tell her that her story is an old one that he has heard a thousand times before. He knows the syndrome well and he has never seen anyone come to a bad end because of it. It never turned into cancer, true colitis, or anything else. Often this is what the patient wanted to know. She can now put up with the discomforts since she knows they are harmless and will recur whenever she gets tense, excitable, or upset.

Similarly, the person with severe sick head aches is often much frightened by them. As a result she is much better when the doctor says "This is a common and well known syndrome. It is not produced by a brain

tumor or anything serious, and it will never bring you to a bad end. It is due to a nervous storm which opens up the arteries in the brain and allows the blood to go pounding through them. You will have much fewer attacks if you can avoid fatigue and nervous strain." Once the patient is convinced of this, she will be half cured. The person who fears heart disease can also be almost cured by a good history which calls his attention to the fact that he has a good wind, so good that he can go hunting and walk miles without distress. This is the best proof that he has an efficient heart.

There are other ways in which the taking of a good history helps. Today, with physicians as busy as they are and with consultant practice as mechanized as it has become, nervous patients are distressed when they are not given time in which to tell their whole story. Too often they are asked only a few questions and then are sent to laboratories and roentgenologic departments and specialists for examinations.

The Examination. Not infrequently another complete examination is not what the person needs, especially when the diagnosis is obvious from the history, and when during the year, several such examinations were made, all with negative results. To most internists today the fact that the person has been carefully examined usually means nothing; they want their own tests and roentgenograms made and they refuse to see the patient until these are all repeated. In some cases of course, some tests should be repeated but when a woman comes with a typical nervous regurgitation, a bad emotional problem, and a lot of roentgenograms showing a beautifully functioning gallbladder, it is hard to see why they should be taken over again. It would seem better, in such a case, to spend little time on examinations and much time in explaining the woman's problem to her and trying to find some way in which she can

difficult and uncomfortable situation. Only in this way will the physician give her good value for the money she pays him.

In most cases of course, the physician will want the patient to have at least one good examination, because even an insane man can have a carcinoma somewhere. All I am objecting to is the senseless repetition of tests that have already been well made and have shown, as was to be expected, that there is nothing wrong in the thorax and abdomen.

Obviously, a good careful examination has great therapeutic value. If the results are negative, a sane patient is immediately cheered and reassured. He may know that he is neurotic or psychoneurotic or troubled and that because of this he can be ill, but he has had the sense to realize that in addition to a neurosis he could have had a carcinoma or a peptic ulcer or a brain tumor. Once relieved of this anxiety he may return home cured.

The Need for Spending Time. Today we physicians are not always giving our nervous patients a square deal. As already noted we are not giving them enough time in which to tell their stories of unhappiness and tragedy and frustration. Often if a patient could get this story off his chest he would be helped. There certainly is such a thing as mental purgation, and the priest helps many a troubled person when he listens to his confession. In the old days we physicians also used this technic, but today too many of us feel that we have no time for it. Even the psychiatrists are becoming so busy and having such enormous demands made upon their time that patients who have been to some of them are complaining that in their offices they did not have a chance to tell their story. They were either just talked to or else turned over to assistants for mental testing. This cannot work well because there never will be any good substitute for conversation between physician and patient, conversation in which the patient does most of the talking.

The physician who limits his interviews to 5 or 10 minutes a patient can never do much in the way of recognizing or curing functional troubles. Even when he gets the correct hunch that the disease is a neurosis and tells the patient it is, he will fail to cure because he has not taken time either to con-

vince the person he is right, or to answer all his objections, or to tell him what to do to get well.

Some Physicians Are Born to be Psychotherapists. There are some men and women with a kindly and sympathetic face to whom men and women can easily tell their troubles. This explains why one physician will quickly get the all important story of, perhaps, worrisome sexual adventures or sins, when several others failed to get it. The physician who draws out his patients' story of tragedy or unhappiness in a kindly and sympathetic way, and particularly the one who has a philosophic outlook will be curing as he listens. He will be radiating confidence and hope. Some men with a dynamic or commanding personality have a strong influence on others, they are born leaders. Naturally when such a man goes into medicine he is likely to be very successful. He can cure hysteria with a bit of suggestion or a quick command, and he can induce many a sick wor-
aga
the
wel
a cl

assistants about him. It helps greatly if he has a big reputation and a number of patients always in his waiting room.

Many physicians are by nature and temperament much too taciturn ever to be helpful to persons with nervous troubles. They will not take time to explain to their patients in simple English what was found or not found and what these things mean, and hence the still worried patients keep traveling about, dissatisfied and unhelped. They were dismissed perhaps with only a few words to the effect that "there is nothing the matter." Especially when a person is fearful that he has a cancer of the stomach or the colon, the doctor should show him his roentgenograms and point out to him the perfectly normal outlines of the organs. He should show him the results of all his tests and explain why they were performed, what they mean, and why they are so reassuring. When this sort of thing is well done the patient may lose his fear and go home cured.

During this process of showing the results of tests, the wise physician will not tell a terribly worrisome patient that he has a func-

tional heart murmur or a few changes in his electrocardiogram a spastic colon or a few diverticula on it a ptosed stomach or things of that nature. If the physician tells the patient of these little variations from normal he and others during the following years may have to spend hours of time trying to explain their lack of significance and to repair the damage done.

Explaining How a Person with Nothing Wrong Can Be Very Ill The next thing that must be done and done expertly is to show the patient how and why a person with negative findings can still be miserable and full of pain. It helps most to give examples understandable to the patient of how a person can vomit or get headache nausea frequent urination diarrhea trembling palpitation or faintness under the influence of acute fear or excitement or emotion. Then one can say "Can't you see now why you who have chronic fear which is worry should suffer too from the effects of your emotion?"

One can explain also how when the brain is too excited undesired influences spread out through the body and as a result the nerves play tricks with a normal heart stomach bowel bladder or skin. Occasionally one can point out to a jittery or depressed man some of whose relatives were insane that what he is suffering from is probably his small share of the family curse. Often one has to explain to the constitutionally frail person the nature of his illness and what he can do to live with it fairly successfully.

Taking Away Placebos of Diagnosis and Treatment One of the first and most important things to do if one is really going to help a psychoneurotic patient is to take away the placebos of diagnosis and treatment which have been given him by the physicians he has already seen. Many persons will not like this process and some will persist in clinging to their placebos. If they choose to do this they had better be dismissed because the physician who likes really to help his patients will with them largely waste his time. For instance let us suppose the physician

heaves that the chronic ache in her loin is due to a dropped right kidney a kinked ureter or a Hunter stricture nothing curative can be done for her. However if she is made to see that she gets the ache every time she goes into a depression or every time her disliked in-laws come to visit her or whenever she stands too long or gets too tired or has a spell of insomnia then something can be done for her.

One must also take away the placebos of treatment from many nervous persons. So long as a man with harmless extrasystoles keeps taking digitalis quinidine or aminophylline every time he is a little frightened or tired he cannot be cured. He can become happy and efficient again only if he accepts the physician's view that the extrasystoles are harmless that the heart is normal that irritable nerves are playing tricks with it that they do this when he is tired or upset and that he needs no heart medicine. Only as he learns to disregard the extrasystoles can he be a well man.

I like what Austen Riggs used to say to a woman when on leaving his sanatorium she came to thank him for having cured her. "No," said he, "You've cured yourself. I only helped you to understand." There are thousands of persons who will cure themselves if we physicians will only help them to understand what their real situation is.

The Patient Who Keeps Shopping About and Getting Frightened There are many persons full of fear of heart disease cancer or something who cannot be helped so long as they keep shopping about from one doctor to another. I always say to the psychopathically anxious man who likes to

over some little notching and slurring and who with his bad diagnosis and prognosis will scare you half to death!

Sometimes I say to such a patient "I referred you to a splendid heart specialist and he told you you have a normal electrocardiogram and a typical cardiac neurosis. Why not accept his statement and be happy?" Unfortunately the man's doubts will usually return and then he will be no more able to keep away from an electro-

same mother before her so long as she be-

cardiograph than a dipsomaniac is able to keep away from a bottle of whisky. And to such a patient an electrocardiogram interpreted by a chiropractor has the same significance as one interpreted by a nationally famous cardiologist.

On Changing a Person's Personality
One reads all the time, in psychiatric journals and books, that the physician must remodel the patient's personality. I wonder if it ever can be done. I even wonder if anyone ever wants his personality changed. Many, of course, would like not to be so tense, jittery, nervous, or unable to fit into society, or to love or be loved, but it's hard for them to mend their ways. Much depends on the person's intelligence and his degree of insight into the situation. I never spend time trying to make over the person who lacks intelligence, who refuses to listen to me, who refuses to accept my view of the situation, who insists on my curing him with a bottle of medicine, who is completely selfish and self-centered or who was obviously born to be a psychopath, a misfit, and a bad actor.

Some Persons Cannot Be Helped
I will work hard to help the intelligent person who has good insight, who is struggling hard to mend his ways, and who seems willing and even glad to be reassured. The man or woman who seems to hate to be reassured is usually not worth working with. Fortunately, long ago, I learned the futility and folly of trying to cure someone against his will.

As I have said, the person with intelligence and a desire to get well can often be helped. He must try hard not to waste his energies on conflicts with himself or with others, and he must learn to hoard his energies. Often he must get more rest; he may need a vacation, he may need to go to bed earlier and sleep longer, and he must try to stop doing many of the things that are hurting him and making him tired and upset. Many a tired, nervous housewife needs a maid much more than she needs a physician.

Things That Can Be Done
Some persons have to take a long vacation, some have to change occupation, and some women will have to separate from an abusive or alcoholic husband. Others straighten out when they see clearly that their illness is due to some unhappy situation or unwise way of living. Occasionally I get a letter from a woman

who says, "I had a rebirth after talking to you, and I feel like a new person. I saw what a mess I was making of my life, and I saw how I could behave myself better. I saw where I was using my prisms to get my own way and to keep from facing unpleasant facts I saw, as you said, that I would never bring myself to divorce my husband. I settled down to be more contented in my home." This is the sort of thing that a sensible woman can do for herself.

The wise physician can tell pretty quickly what type of patient he can help and what type he cannot help. As I have said, among those he cannot help are the highly opinionated ones who know it all and will hardly listen to what he says. Many are caught in a miserable trap from which neither they nor I can see any way of escape. I'm thinking of, let us say, a secretary who is tired out working in an unpleasant job, but who cannot quit because at home she has an old arteriosclerotic, and ailing mother who has to be cared for.

Because of these difficult situations in which our patients find themselves, we physicians must always make our advice practical. It's useless to tell the poor scrubwoman with half a dozen fatherless children to go to Florida for the winter. Sometimes, however, by talking to the patient, one can find out certain things that he can do in order to get some rest and some relief.

Often one of the first things one has to do with a nervous woman is to make her see that there is nothing to be ashamed of in being tense and hypersensitive. She might even be proud of her sensitiveness and reactivity, especially if they enable her to be a good musician or artist or an interesting companion to her husband. In many cases I have to point out to a patient that she is hypersensitive and overreactive, that her knee jerks are tremendously exaggerated, and that any person who reacts as violently to every little stimulus must be tired by the end of the day.

As one would expect, the physician who has suffered from nervousness can cure nervous persons much more easily than can one who has never suffered in this way. The stolid insensitive physician finds it hard to understand how nervous persons can be so "silly." He may have no patience with them.

and no desire to listen to their tales of woe. He may even think they are making their illness out of whole cloth. Naturally when a woman discovers that her physician has also suffered from nervousness she is much easier in her mind and more willing to talk because she knows she will not be sneered at or called offensive names.

The Value of Optimism It is always good if the physician is an optimist. Too many of us are inclined to pessimism and hence we often fail to cure. For instance if a man comes in frightened because he has been told that he has had a coronary thrombosis it is wise to tell him of those thousands of men who are still at work 10 and 15 years after such an incident. Sometimes an elderly person comes in much frightened because he has had a slight stroke. Because of some folk idea he expects in the next few months to have another and then the third big one that will kill him. I promptly tell him of patients I have known who after a little or a fairly big stroke waited 15 years for another one. I tell of a man I knew who lived 30 years after he had had several little strokes severe enough to cause his retirement from business. When a patient comes in much frightened about hypertension I tell of some of the many persons I have known who with a systolic pressure over 200 mm of mercury lived on for 15 or 20 years comfortably enough. Why should not the patient know of these cases? Why should he be informed only of the disasters which can happen to him?

The Need for Positive Statements As I have already remarked one of the worst features of medical treatment is the tendency of many physicians to sidestep unqualifiedly

that he can walk 20 blocks without discomfort. The electrocardiogram shows no changes to indicate myocardial damage. Under these circumstances my colleague

I can find you have absolutely no sign of heart disease. I suspect your physician mistook for something serious little changes in

your electrocardiogram which in our experience are of no consequence. They are the results of age like your gray hair. Go ahead now and enjoy life. Walk along the street cheerfully as you have always done. Play golf if you feel like it and do not worry about your heart."

With this positive statement many a patient would
 would
 ct him
 in had
 hedged and said: "I think you're all right but you had better play safe. Here is some digitalis and don't go upstairs fast. Don't walk much. Don't play golf and don't drive your car."

Similarly no physician can cure hysteria unless he is positive in his statements. If he says "That stiff arm of yours may possibly be of hysterical genesis and it's just possible that you might be able to move it" but then again "I may be mistaken" he will not get anywhere.

What he must do is to say the minute he sees the arm held in a hysterical position "Why that's a typical case of a nervously weakened arm. I have cured hundreds of them in a few minutes. Your muscles and nerves are perfectly all right; you've just lost confidence in them. See your fingers move a little. If the nerves were gone you couldn't do that. See also you can feel. If the nerves were gone you couldn't do that. Come now start moving the arm and in a few minutes you will be able to move it well. Soon you will be all right."

Then the patient is likely to start moving the arm.

What the Patient Can Do The patient often says "Well supposing I am nervous or a bit psychoneurotic what can I do to help myself?"

The first thing to do is to begin right away to learn to face difficult things and to tackle problems and to solve them quickly. If a man lives sanely and thinks sanely he is likely to stay sane. He must try also to live by one of Osler's wisest maxims which was to "live each day in day tight compartments worrying little about the morrow and wasting no regrets over the mistakes and sorrows of the past." Another of Osler's great bits of advice was to "burn your own smoke", to keep quiet about discomforts and not inflict

constant recitals of them on everyone who will listen

Many persons, if they set their minds to it, could get away from some of their difficult situations. Many would be better if they could only make up their minds what they are going to do about their handicaps and frustrations. Many a woman who is fretting and worrying herself into illness could get well if she would stop thinking only of herself and try to do things for her neighbors and her city. Sometimes a man can get better if he finds a hobby that will keep him busy in his spare time.

So many people get into trouble because they do everything hurriedly and with strain. They should try to work without such feelings of tension and hurry. For instance, a bank teller admitted that he broke down and went to pieces whenever the line in front of his window got beyond a certain length. I said to him, "Why look at the line?" Just look at the man at the window and attend to his business as if he were the only man in the bank."

Worry. One of the greatest troubles of many persons is their tendency to worry foolishly. Often of course, they have good reasons to be worried and then we physicians should not tell them aimlessly to "forget it." If we were in their predicament we would worry, too. But many a worrisome woman has not much to worry about, and we can then admonish her and urge her to mend her ways.

Austen Riggs had good advice for worriers. He said, "Note if the problem is yours to solve. If it isn't, and you can't do anything about it, obviously you shouldn't worry about it."

For instance here is a woman who is worrying herself sick because her daughter does not get engaged to a certain man. If she would only admit that the problem is not hers but the daughter's she might be able to stop worrying and go about her business.

The next question for a worrier is: If it is your problem can you tackle it and solve it now? If so then it ought to be tackled right away. If it can not be tackled now, then wait until it comes up for solution. Furthermore, if the problem is one that can and should be solved with the help of expert advice, then

one should get it quickly, perhaps from a lawyer, a banker, or a physician.

Finally, when the decision is made, the subject should be closed. One of the greatest troubles of many persons is that after they have made a decision, they keep re-opening the matter again and again. Far better is a poor decision quickly made and abided by than a better one not made, or if made, not adhered to. I often remind a woman that I have to make big and important decisions all day and quickly, without worrying about them. Why should she not learn to make her small decisions about the home quickly and finally? It would save her much worry and fatigue and unhappiness.

Often a woman frets herself into illness trying to make up her mind about a divorce. I say to her, "Here is an imaginary button on the end of my desk, press it now and you'll be back from Reno with your decree in your hand."

If she refuses to press the imaginary button, I say, "There you are, you do not really wish to get that divorce or you are not tough enough to hurt others, or to face the world alone, so stop thinking about it and settle down to make a better go of your marriage."

Conflict with Others. Many persons are upset much of the time because they keep getting into needless arguments or fights with people about them. Mothers are constantly clashing with their children or with the husband, and these conflicts are tiring. A more sensible or thoughtful or self-controlled person would probably never have started any of the rows. She would not have told her boy not to go out to play when there was no good reason why he should not have gone. To mothers I say, "Try never to start anything with your children unless you feel that it is very important to correct their behavior or to keep them from doing something that they much want to do."

So often when a child wants to go some where the mother says "No" and that starts a long argument and a clash of wills which leaves the woman tired and almost ill. Usually her only reason for interfering with the child's plans was that she would worry until he or she came home.

A kindly, friendly, courteous, tactful and sensible man can work for months with his

colleagues or employees without ever uttering a harsh word or getting into open conflicts. He will mind his own business, he will not bother other people, and he will not try to take away their prerogatives. He will always yield on nonessentials and will let the other fellow have his way whenever possible. He will not try to run the lives of those about him. If he ever has to correct an employee, he will do it with kindness and tact and not before others.

Childish Behavior. Most of the troubles in the home and perhaps in the office are due to childish behavior. Hence it is that every man and woman should strive to act always like a grown up.

Much of a mother's annoyance and strain are due to the poor discipline of her children, and this is usually her own fault. If she never asked them to do anything unless there was a good reason for it, and then if she saw to it that they obeyed quickly and courteously, life would be much easier for the children as well as for her. Too often the mother gives endless orders that are never obeyed, and then after years of this she wonders why she is treated without respect. If only mothers would not "start something" when they have not the strength, the pertinacity, or the right on their side to carry it through.

Excessive Shyness. Many of the troubles of slightly psychopathic persons in this world are due to their shyness and self-consciousness, their feelings of inferiority, and the strain of meeting their fellows. With help from a wise physician, some of this shyness can be overcome. Many a shy young woman has been helped by being told by the physician that she, with her good looks, trim body, good education, and courteous ways, has no reason to feel inferior. Sometimes such feelings of inferiority have been built up by a jealous stepmother or a sadistic brother or an ignorant husband.

On Getting Rest. One of the most important things many a nervous person needs to do is to learn to get more rest.

Persons putter around until midnight or later when they could easily be in bed or asleep by 10 o'clock. Many spend their Saturday afternoons and Sundays doing too much

Any so-called recreation which leaves a man or woman rested is good, whereas anything that leaves him or her more tired and more nervous and tense is bad.

It may take some argument to get a woman to try to rest. She will feel that she will be a bad mother and a bad wife if she takes time out to rest. I often tell such a woman that she who so wants to be a fine mother is being a poor one because she is too irritable to get along with her children. With a few weeks of rest, perhaps at a sister's, she could be a new woman. Occasionally when a woman is tired out and at the end of her rope, a sort of Weir Mitchell cure in a sanatorium will do most good if it can be secured or afforded.

Treatment with Drugs. There is not much in the way of drug treatment for persons who are nervous and tired. Many physicians give phenobarbital or bromides three times a day, and sometimes this helps and gives some comfort, but I dislike to start persons on such a habit. It would seem better to have the patient take a sedative only

sleep, he or she is likely to get better. In my experience, the use of barbiturates is not dangerous, and no one who has any sense will ever become habituated to these drugs. In 40 years I have never seen them produce enslaving habituation comparable to that which often follows the taking of opiates.

There are quite a few persons who get to sleep easily enough at bedtime but who wake about 4 in the morning and then can not drop off again. I give those persons bromural because it is a quick-acting drug and its effect is likely to be over in 2 or 3 hours. Under these circumstances a person who has taken it can get up at 7 with a clear head.

Treatment by Psychiatrists. Only the patients with the worst neuroses or psychoses are likely to need the help of a psychiatrist or are likely to consent to go to one. Needless to say, psychiatrists could help many of our other nervous patients, but there are not enough of these specialists to go around. There are only a few thousand of them to care for the millions of the neurotic and psychopathic. Obviously, then, nearly all of

the handling of nervous patients must be done by nonpsychiatric practitioners. The big problem today is to teach these physicians to recognize neuroses and psychoses when they see them.

Unfortunately many of the neurotic patients who cannot be helped by the nonpsychiatrically trained physician cannot be helped even by the psychiatrist. They are the persons with a low intelligence quotient, marked hypochondriasis, marked depression, a tendency toward schizophrenia, or a psychopathic personality which gets them into one scrape after another. Most of the persons with a psychopathic personality are too self-centered and selfish ever to be reached by any type of therapy. Others do well when sheltered and kept away from a troublous world but, when they go back home to strains and annoyances and too much alcohol they break down.

The wise and experienced physician can usually tell within a few minutes the type of patient he can help and the one he cannot. Usually he can learn most about the seriousness of a patient's mental situation by talking to the spouse and other long suffering members of the family. They alone may tell of insane, antisocial or unreasonable behavior, terrible wastage of the financial resources of the relatives, alcoholic sprees, disgraceful sexual episodes or violent outbursts of temper. Many a time I have seen a person of this psychopathic type who had spent years in the hands of surgeons and others getting operated on and treated for this and that. If one of these physicians had ever interviewed the family and got them to talk freely he would have been astounded to learn that his patient was insane.

WALTER C. ALVAREZ

CEREBRAL EMBOLISM, THROMBOSIS AND HEMORRHAGE INCLUDING CEREBRAL ARTERIOSCLEROSIS

The treatment of the manifestations of any one of these three cerebral circulatory disturbances requires first of all their diagnostic differentiation. Aring and Merritt's clinical and pathologic study as well as many other contributions to the literature have been devoted to this task but the fact remains that the differential diagnosis is not

always feasible. Embolism is usually diagnosed in younger individuals with evidence of heart disease, mostly rheumatic, often with evidence of other embolic lesions in the retinal arteries or elsewhere in the body. Yet many arteriosclerotics, with or without

of little diagnostic value since each may be affected by cerebral edema, reflexory changes in the cerebral circulation or, nat

accompanied by loss of consciousness. In doubtful cases, a history of essential hypertension will suggest cerebral hemorrhage. Blood in the spinal fluid is occasionally present in massive hemorrhage when the inter cerebral hemorrhage has perforated into the ventricular system or into the intra arachnoid space. Increase of spinal fluid pressure over 160 mm of water is often seen in cerebral hemorrhage. The complicating subarachnoid hemorrhage betrays itself frequently by rigidity of the neck and leukocytosis in the blood may be seen as a reaction to the hemorrhage.

Some of the neurologic findings in circulatory brain lesions are helpful in differential diagnosis. Thrombosis, seldom embolic, encephalomalacia is often localized in the posterior parts of the brain irrigated by the cerebri posterior, and produces hemianopsia without hemiplegia. Hemorrhages rarely occur in this area. Evidence of circulatory lesions in the brain stem, cerebellum and circumscribed cortical areas (persisting aphasia, monoplegias), as well as of multiple brain lesions indicates ischemia, mostly of thrombotic origin. Hemorrhages in the cerebellum are rare. Wilson gives their percentage as about 01 per cent of brain hemorrhages. Signs of cerebral irritation in the form of epileptic seizures are usually found in ischemic cortical lesions and in cerebral arteriosclerosis (mostly in hypertensive patients) but also may be found in embolism.

followed by viral

n.

an

a perforating hemorrhage accumulates over the cortex or seeps into the ventricles. In the latter case decerebrate rigidity and tonic extensor fits are often seen.

The course and prognosis of the three cerebral vascular lesions are in general somewhat different although here again the individual case may not correspond to the rule. Cerebral embolism and thrombosis have a smaller mortality percentage (about 50 and 30 per cent respectively) whereas massive hemorrhages are fatal in almost 80 per cent. In embolism the initial loss of consciousness may be overcome within a few days but in massive hemorrhage a few patients a few

consciousness. A fatal course in cerebral thrombosis owing to the gradually increasing encephalomalacia or to a complicating circulatory failure or to bronchopneumonia seldom leads to death under a week's time and the patient's fate may remain precarious for a month. Many patients with cerebral arteriosclerosis suffer in their lifetime from multiple ischemic lesions which by no means always appear clinically as "strokes." Textbooks on neurology and psychiatry describe a variety of syndromes that may occur in cerebral arteriosclerosis.

The clinical pathology of circulatory brain lesions consists of an effusion of blood through damaged vessel walls in patients suffering from essential hypertension in a so-called massive brain hemorrhage and of an ischemia of the brain in patients suffering from arterial embolism or from an arteriosclerotic encephalopathy. In many instances the effects of arteriosclerotic and degenerative weakening of the vessel walls in hypertension (described as hyalinosis) are combined. Therefore a hypertensive patient often suffers from multiple ischemic brain lesions before a massive hemorrhage occurs. Treatment ought to consider that extreme variations of blood pressure in the earlier stages of a

certain aortic lesions rarely precipitates a brain hemorrhage. On the other hand cerebral ischemia in arteriosclerosis often follows a drop in blood pressure which explains the frequency with which such patients suffer strokes during the night or under the effect of heart failure. In fact encephalomalacia in cerebral arteriosclerosis is by no means always caused by a visible arterial thrombosis as many pathologists have found but is often the effect of tissue anoxia in areas of the brain insufficiently irrigated in the presence of arteriosclerotic narrowing of the vessel lumen particularly at the sites of the branching off of the smaller arteries from the large basilar vessels.

Much has been written about arterial spasms contributing to cerebral damage in the hypertensive and arteriosclerotic group of vascular brain lesions. One may safely assume that a certain number of transient

in hypertensive patients may be caused by vascular spasms. This belief arises from the success of antispasmodics in some of these cases. Their effect is usually of a prophylactic character because the purely functional contraction of an artery is of short duration only and the longer lasting impairment of brain function is probably due to postspastic tissue edema. Apparently transitory brain lesions of days or weeks' duration so frequently seen in hypertensive or arteriosclerotic patients should be accepted as evidence of organic tissue damage mostly small ischemic foci the occurrence of which betrays organic vascular damage and not a purely functional vascular spasm. The importance of vascular spasms appears to be much greater in the extensive cerebral ischemia that follows arterial embolism. Here a reactive spastic contraction of the suddenly embolized artery is combined with functional disturbances of the arterial and venous blood flow over a wide area leading first to cerebral edema and finally to ischemia with softening of the brain tissue.

The early or prophylactic treatment of circulatory brain disturbances is the more desirable since any severe type of vascular damage will show itself in the impairment or loss of certain cerebral functions, which

is of more ominous significance than the high systolic pressure. Increased systolic pressure without rise of diastolic pressure, as often seen in old arteriosclerotics or in

in time may become compensated to a variable degree but can never be cured

Prophylaxis of Cerebral Hemorrhage
The ideal solution to this difficult problem is to stop the fateful progress of the arterial hypertension. By what means this can best be achieved is discussed elsewhere in this book. Thoracolumbar sympathectomy will often have to be considered and every experienced physician knows how difficult a decision this is in view of the fact that lasting results can never be predicted. It may be interesting to know that surgeons such as M. M. Peet and J. L. Poppen do not regard cerebrovascular accidents as contraindications in themselves although Peet requires his patients preferably under 50 years of age to have recovered completely from their vascular lesions. American as well as European surgeons have reported a goodly number of patients with cerebrovascular accidents before sympathectomy with recurrences in only about 10 per cent. That patients occasionally suffer strokes during a sympathectomy indicates the necessity of evaluating the severity of true arteriosclerotic lesions of the cerebral arteries. This may be facilitated by roentgenographic study of the skull and by arteriography. Indirectly one may conclude that coronary sclerosis particularly in hypertensives is frequently associated with cerebral arteriosclerosis. It is not surprising that this group of cases with early ischemic lesions in heart and brain succumbs to the rapid lowering of the blood pressure after sympathectomy. The state of the retinal arteries and the degree

of the

decide whether or not sympathectomy is indicated. One may agree with R. S. Palmer that sympathectomy is the treatment of choice for patients with malignant hypertension in the presence of retinopathy with papilledema after dietary and medical treatment have failed to improve the condition. Like Poppen and Lemmon we feel especially that cases classified as grade IV retinopathy with choking of the optic disks and retinal hemorrhages occurring in relatively young patients and with a fulminating or rapidly progressing hypertension demand immediate operative intervention. Even

grade IV retinopathy may disappear and not return for some time after sympathectomy. As Peet has stated it is a fact that malignant hypertension with grade IV neuroretinopathy predicts an extremely serious course of the disease often terminating in massive cerebral hemorrhage, an event which at least in a certain number of selected cases can be prevented or postponed by dorsolumbar sympathectomy. On the other hand one should bear in mind also that milder cases of arterial hypertension with grade I or II neuroretinopathy and with no stabilization of high blood pressure may succumb to a cerebral hemorrhage. It is here where the clinical picture before the hemorrhage does not appear to be threatening that the decision in favor of a sympathectomy will be particularly difficult. We think that it should be postponed until all other therapeutic measures have been exhausted.

Venesection for the prevention of cerebral hemorrhage has been generally abandoned and as it seems to this author not quite justly. Particularly in hypertension with polycythemia it should be considered. Edwards and Bordenave found that the removal of 500 cc of blood was followed by a fall in blood pressure lasting for about 3 months and accompanied by an improvement in the subjective symptoms (see also below).

Short transient pareses and paralyses in patients with arterial hypertension (and occasionally in those without) may be prevented or more rapidly overcome by vasodilating drugs. Papaverine may be given intravenously if rapid action is desired in doses of 0.03 to 0.06 gm. By mouth 0.1 gm three times a day is the minimal effective dose. Its low toxicity permits even higher doses. One may combine papaverine with 30 mg of phenobarbital or aminophylline. The latter injected slowly can also be given intravenously in doses of from 0.3 to 0.5 gm.

Treatment It is extremely important to recognize the early symptoms of circulatory insufficiency of the brain. In many instances the initial stage shows a clinical syndrome which is best described by the term "pseudoneurasthenia." The diminution of mental alertness, the impairment of energy, concen-

tional tension, hypochondria, depression, etc—all these manifestations which may or may not terminate in the picture of an arteriosclerotic dementia reveal themselves often before neurologic signs of a cerebral circulatory decompensation make their appearance. Classical symptoms and signs of the latter include headache, sometimes combined with paresthetic sensations in the chest abdomen, or extremities, an occasional feeling of dizziness, sometimes of true vertigo often with slight impairment of hearing, fainting spells, disturbance of sleep, and the various focal motor or sensory pareses including speech and other disorders which follow the many ischemic (less frequently the hemorrhagic) lesions of the brain.

Patients with early signs of cerebral arteriosclerosis or those in the presclerotic phase of hypertension often respond well to the common sense laws of mental and physical hygiene—reduction of activities, interpolation of rest periods such as one hour of bed rest after lunch, periodic vacations, lessening of responsibilities, regular and moderate dietary habits, and avoidance of exhaustion. Although the noxious effect of nicotine in arteriosclerosis is debated, the extent to which smoking may contribute to the causation of certain symptoms particularly those of headache and dizziness, should be investigated. If the discontinuance of smoking brings about disappearance or mitigation of symptoms, then complete abstinence from nicotine should be recommended. Alcohol, too, is often poorly tolerated by these patients and, if taken at all, should be consumed only in great moderation. Dietary measures should be directed against so-called heavy and highly spiced food, and should provide for light meals especially at night, since overloading of the intestinal tract favors brain anemia. Overweight is another condition often associated with premature arteriosclerosis, and intelligent gradual reduction of obesity often has a beneficial effect.

HEADACHE. The treatment of recurrent headaches of arteriosclerotic and hypertensive patients is often a problem although many patients take these headaches lightly since they show a spontaneous tendency to disappear once the patient is out of bed and has put cold water on his face. These

headaches may be subdivided into a tem-poro-frontal pain, with all the characteristics of a migraine, and a severe ache in the nape of the neck radiating over the occiput up to the vertex and downward over the shoulders. Patients with the latter type often complain of an unpleasant sensation which they describe as that of a tight band or cap around the head, as if the head were in a vise.

As the result of a dilatation and a distention of branches of the external carotid artery the temporal as well as the middle meningeal arteries, the frontotemporal pain corresponds to all appearances, to the true migrainous headache. Yet, only about half

these headaches become more frequent. However, there is no parallel between the fluctuations of the blood pressure and the headache, and quite a few patients lose these headaches with mounting pressure, especially after the occurrence of vascular brain lesions. Wolff's explanation of these headaches as the combined effect of stress, fatigue and other conditions leading to a decrease in vascular tone and distention plus the dilatating effect of increased blood pressure is borne out by everyday observations. Treatment of these headaches should consist first of all in having the patient avoid all possible situations which might affect unfavorably the contractile state of his arteries. This is most important, since the painful condition of the branches of the external carotid artery is probably accompanied by undesirable and ultimately harmful tonus changes in the cerebral arteries. Even more important than the medical management are those therapeutic measures dealing with the patient's way of living and working as well as with his emotional attitudes, his frustrations, his maladjustments, and often with present neurotic

these patients have already been mentioned. The psychologic problems of these patients can well be left to the patient's understanding and wise counselling of the general practitioner, except where the personality conflict

is such as to indicate more intensive treatment by a psychiatrist. All of us have seen many arteriosclerotic and hypertensive patients lose their migrainous headaches with a change of certain detrimental habits with the instituting of a more wholesome life and with the overcoming of their neurotic ways of dealing with their problems.

The medical treatment of these migraine like headaches follows the same principles outlined in the chapter on migraine with the difference that ergotamine tartrate may be used only if the patient is not suffering from marked organic changes of the arteries. The same holds true for all those agents which like ephedrine, benzedrine, epinephrine and pituitrin have a constricting effect on blood vessels but at the same time increase systemic pressure. Only caffeine 0.3 to 0.6 gm given by mouth or as a cup of strong hot coffee may be used although while some patients feel relieved by it others feel worse. Of all the agents which act by raising the pain threshold, acetyl salicylic acid (0.5 to 2.0 gm in tablets) or if necessary codeine phosphate (0.06 gm) are most satisfactory. To prevent these headaches after a hectic day with its numerous strains or after a prolonged evening with its overstimulation, satisfactory general relaxation and sounder sleep may be gained with 0.1 gm of phenobarbital, 0.2 gm of sodium amytal or 0.1 gm of nembutal. Also a combination with 0.5 to 1.0 gm of aspirin may be tried. Many patients with cerebral arteriosclerosis show symptoms of mild depression associated with anxiety particularly after strenuous mental activities and these individuals benefit from taking 0.06 to 0.1 gm of powdered opium in capsules at bedtime only or if necessary two or three times during the day after meals. The danger of addiction is negligible.

The occipital and skull pain with or without temporofrontal headache may be a harmless muscular pain due to spastic muscular contraction (see the chapter on Headache where the treatment of these pains is discussed). When associated with migrainous headache it frequently reacts to the medication just described. Many of these patients who complain of occipital headaches when resting on a feather pillow are relieved

when change is made to a horsehair pillow. Occurring in arteriosclerotics without hypertension during the early morning hours or with mental fatigue the pain may be due to a certain degree of brain anoxia possibly combined with increase of venous pressure. Improvement of cerebral circulation can be achieved by avoidance of strain and by mild physical exercise. General recommendations such as these should be complemented by a more specific support of the general circulation when necessary.

In the final stages of malignant hypertension for the most part those with renal failure and stage IV retinopathy another type of headache may occur more lasting not limited to the morning hours and often associated with nausea and vomiting. These headaches are seen in patients with so much evidence of organic vascular damage that with or without evidence of focal brain lesions their causation by a hypertensive encephalopathy must be assumed. This condition not rarely complicated by epileptic seizures shares with the so called hypertensive crises the occurrence of vascular spasms or organic ischemic cerebral conditions followed by edema of the brain. Renal insufficiency with azotemia may or may not complicate this condition. The often severe headache reacts to a lowering of the generally increased intracranial pressure. Repeated spinal punctures (at least 20 cc) have proved helpful in a number of cases as has also the intravenous infusion of hypertonic solutions (see below). Dietary measures especially a low sodium diet are recommended.

Prevention of Cerebral Embolism. The prophylaxis of embolic brain lesions concurs with the prevention of thrombus formation as the source of emboli e.g. with the successful management of a rheumatic heart the most frequent source of embolism particularly in younger persons. This and the use of anti-coagulants (dicumarol and heparin) in thrombus formation are described elsewhere.

The treatment of apoplexia or what is generally understood as a stroke is usually regarded as symptomatic. Yet the degree of recovery of many a hemiplegic depends on the medical attention and nursing care given to these patients. In addition it is possible

to affect the deranged cerebral circulation by certain active therapeutic measures

Embolie encephalopathy and certain cases of cerebral thrombosis may respond to infiltration of the stellate ganglion with an esthetics. Gilbert and de Takats have come to the conclusion that in cerebral embolism injections made at the earliest possible moment will accelerate the phase of restitution. De Takats' method of treatment follows

The patient's neck is slightly hyperextended by a small pillow placed under the shoulder

injection of a $\frac{1}{2}$ per cent solution of procaine hydrochloride (without epinephrine) a dermal wheal is placed over the tip of the seventh transverse process then a 4 inch (9 cm.) 22 gauge needle is inserted through this wheal. It must shortly make contact with the tip of the transverse process, which is quite superficial. Then the needle slides along the superior border of the transverse process until it contacts the body of the sixth cervical vertebra. Aspiration is now made for air bubbles for blood for spinal fluid, and if none of these is observed 10 cc of a 1 per cent solution of procaine hydrochloride is injected aspirations being made repeatedly during this procedure.

A successful block is followed within 10 to 15 minutes by Horner's syndrome by dilatation of the conjunctival vessels, by dryness and increased warmth of the face and ear lobes on the side of injection and by rising temperature and dryness of the corresponding upper extremity.

the next 10 minutes the improvement may then continue

Recently Amyes and Perry* have reported on "stellate ganglion block in the treatment of acute cerebral thrombosis and embolism." They have used the anterior approach to anesthetize the sympathetic chain and the

anterior approach is also easier than the

lateral one. One inserts a 22 gauge needle without a stylet close to the edge of the trachea about two finger breadths above the sternal notch, after anesthetizing the skin with a small amount of a 2 per cent procaine hydrochloride solution. The patient relaxes in a supine position and the needle is directed posteriorly, perpendicular to the cervical spine. As the needle passes through the tissues one has to make sure by aspiration that no blood vessel or the pleural cavity, or finally the subarachnoid space has been entered. Upon reaching the bone 10 cc of a 1 to 2 per cent aqueous solution of procaine hydrochloride are injected.

The results of stellate blocks are more encouraging in embolism than in thrombosis and better in younger than in old patients. The latter observation can well be explained by the defective brain tissue regulation of the capillary blood flow in the presence of severe cerebral arteriosclerosis. The block should be performed shortly after the stroke, possibly within the first 24 hours. Yet even after days or a few weeks some clinical improvement can be obtained. The block may be repeated daily or after longer intervals so long as a beneficial effect is observed as well as in cases of repeated cerebral insults. The risk involved is so little that the recommendation of Amyes and Perry to make the stellate block a "routine treatment by well trained persons for acute cerebral thrombosis or embolism" deserves serious consideration. Patients suffering from more or less transient cerebral palsies indicating increasing localized ischemic disturbances may occasionally benefit from a stellate block as a preventive measure, to counteract the narrowing of an artery by improving the collateral and capillary circulation. A simultaneous bilateral block is said to be dangerous, and Amyes and Perry recommend waiting at least 4 hours between blocks.

Wernicke has already suggested the surgical removal of blood clots after massive hemorrhage, and many of us, likewise, have thought of saving a patient from the effect of a hemorrhage by removing the blood. Ever so often favorable reports of such a procedure appear e.g., W. H. Hamby's series of 16 surgically treated cases, with 14 recoveries. Surgery is considered in cases with apoplectic or with gradual onset, where there

* Amyes E. W., and Perry S. M. Stellate Ganglion Block in the Treatment of Acute Cerebral Thrombosis and Embolism. J. A. M. A. 142:15, 1930.

is such as to indicate more intensive treatment by a psychiatrist. All of us have seen many arteriosclerotic and hypertensive patients lose their migrainous headaches with a change of certain detrimental habits with the instituting of a more wholesome life and with the overcoming of their neurotic ways of dealing with their problems.

The medical treatment of these migraine like headaches follows the same principles outlined in the chapter on migraine with the difference that ergotamine tartrate may be used only if the patient is not suffering from marked organic changes of the arteries. The same holds true for all those agents which like ephedrine, benzedrine, epinephrine and pituitrin have a constricting effect on blood vessels but at the same time increase systemic pressure. Only caffeine 0.3 to 0.6 gm given by mouth or as a cup of strong hot coffee may be used although while some patients feel relieved by it others feel worse. Of all the agents which act by raising the pain threshold, acetylsalicylic acid (0.5 to 2.0 gm in tablets) or if necessary codeine phosphate (0.06 gm) are most satisfactory. To prevent these headaches after a hectic day with its numerous strains and after a prolonged evening with its overstimulation, satisfactory general relaxation and sounder sleep may be gained with 0.1 gm of phenobarbital, 0.2 gm of sodium amytal or 0.1 gm of nembutal. Also a combination with 0.5 to 1.0 gm of aspirin may be tried. Many patients with cerebral arteriosclerosis show symptoms of mild depression associated with anxiety particularly after strenuous mental activities and these individuals benefit from taking 0.06 to 0.1 gm of powdered opium in capsules at bedtime only or if necessary two or three times during the day after meals. The danger of addiction is negligible.

The occipital and skull pain with or without temporofrontal headache may be a harmless muscular pain due to spastic muscular contraction (see the chapter on Headache where the treatment of these pains is discussed). When associated with migrainous headache it frequently reacts to the medication just described. Many of these patients who complain of occipital headaches when resting on a feather pillow, are relieved

when change is made to a horsehair pillow. Occurring in arteriosclerotics without hypertension during the early morning hours or with mental fatigue the pain may be due to a certain degree of brain anoxia possibly combined with increase of venous pressure. Improvement of cerebral circulation can be achieved by avoidance of strain and by mild physical exercise. General recommendations such as these should be complemented by a more specific support of the general circulation when necessary.

In the final stages of malignant hypertension for the most part those with renal failure and stage IV retinopathy another type of headache may occur more lasting not limited to the morning hours and often associated with nausea and vomiting. These headaches are seen in patients with so much evidence of organic vascular damage that, with or without evidence of focal brain lesions, their causation by a hypertensive encephalopathy must be assumed. This condition not rarely complicated by epileptic seizures shares with the so called hypertensive crises the occurrence of vascular spasms or organic ischemic cerebral conditions followed by edema of the brain. Renal insufficiency with azotemia may or may not complicate this condition. The often severe headache reacts to a lowering of the generally increased intracranial pressure. Repeated spinal punctures (at least 20 cc) have proved helpful in a number of cases as has also the intravenous infusion of hypertonic solutions (see below). Dietary measures especially a low sodium diet are recommended.

Prevention of Cerebral Embolism. The prophylaxis of embolic brain lesions concurs with the prevention of thrombus formation as the source of emboli e.g. with the successful management of a rheumatic heart the most frequent source of embolism particularly in younger persons. This and the use of anti-coagulants (dicumarol and heparin) in thrombus formation are described elsewhere.

The treatment of apoplexia or what is generally understood as a stroke is usually regarded as symptomatic. Yet the degree of recovery of many a hemiplegic depends on the medical attention and nursing care given to these patients. In addition it is possible

to affect the deranged cerebral circulation by certain active therapeutic measures

Embolie encephalopathy and certain cases of cerebral thrombosis may respond to infiltration of the stellate ganglion with anesthetics. Gilbert and de Takats have come to the conclusion that in cerebral embolism injections made at the earliest possible moment will accelerate the phase of restitution. De Takats' method of treatment follows:

The patient's neck is slightly hyperextended by a small pillow placed under the shoulder

Injection of a 1 per cent solution of procaine hydrochloride (without epinephrine) a dermal wheal is placed over the tip of the seventh transverse process, then a 4 inch (9 cm) 22 gauge needle is inserted through this wheal. It must shortly make contact with the tip of the transverse process, which is quite superficial. Then the needle slides along the superior border of the transverse process until it contacts the body of the sixth cervical vertebra. Aspiration is now made for air bubbles, for blood for spinal fluid and, if none of these is observed, 10 cc of a 1 per cent solution of procaine hydrochloride is injected, aspirations being made repeatedly during this procedure.

A successful block is followed within 10 to 15 minutes by Horner's syndrome, by dilatation of the conjunctival vessels, by dryness and increased warmth of the face and ear lobes on the side of injection, and by rising temperature and dryness of the corresponding upper extremity. If Horner's syndrome does not develop the injection must be regarded as faulty and should be repeated. If improvement is to follow cervical sympathetic block it should be noticed within the next 10 minutes, the improvement may then continue.

Recently Amyes and Perry* have reported on "stellate ganglion block in the treatment of acute cerebral thrombosis and embolism." They have used the anterior approach to anesthetize the sympathetic chain and the stellate ganglion. I have found this approach successful where probably for anatomic reasons, the lateral approach had failed. The anterior approach is also easier than the

lateral one. One inserts a 22 gauge needle without a stylet close to the edge of the trachea about two finger breadths above the sternal notch, after anesthetizing the skin with a small amount of a 2 per cent procaine hydrochloride solution. The patient relaxes in a supine position and the needle is directed posteriorly, perpendicular to the cervical spine. As the needle passes through the tissues, one has to make sure by aspiration that no blood vessel, or the pleural cavity, or, finally, the subarachnoid space has been entered. Upon reaching the bone 10 cc of a 1 to 2 per cent aqueous solution of procaine hydrochloride are injected.

The results of stellate blocks are more encouraging in embolism than in thrombosis, and better in younger than in old patients. The latter observation can well be explained by the defective brain tissue regulation of the capillary blood flow in the presence of severe cerebral arteriosclerosis. The block should be performed shortly after the stroke, possibly within the first 24 hours. Yet even after days or a few weeks some clinical improvement can be obtained. The block may be repeated daily or after longer intervals so long as a beneficial effect is observed, as well as in cases of repeated cerebral insults. The risk involved is so little that the recommendation of Amyes and Perry to make the stellate block a routine treatment by well trained persons for acute cerebral thrombosis or embolism* deserves serious consideration. Patients suffering from more or less transient cerebral palsies indicating increasing localized ischemic disturbances may occasionally benefit from a stellate block as a preventive measure, to counteract the narrowing of an artery by improving the collateral and capillary circulation. A simultaneous bilateral block is said to be dangerous, and Amyes and Perry recommend waiting at least 4 hours between blocks.

Wernicke has already suggested the surgical removal of blood clots after massive hemorrhage, and many of us, likewise, have thought of saving a patient from the effect of a hemorrhage by removing the blood. Ever so often favorable reports of such a procedure appear, e.g., W. H. Hamby's series of 16 surgically treated cases, with 14 recoveries. Surgery is considered in cases with apoplectic or with gradual onset, where there

* Amyes E. W., and Perry, S. M. Stellate Ganglion Block in the Treatment of Acute Cerebral Thrombosis and Embolism. *JAMA*, 142:15, 1950.

is a progression of signs and development of evidence of increased intracranial pressure. As a procedure less drastic than craniotomy, trephine aspiration of the clot has been recommended but, of course, aspiration does not eliminate the solid clots present in most hematomas. Contraindications to surgical removal of the hematoma include not only the usually poor condition of the patients with massive brain hemorrhage, but more especially the fact that almost every otherwise fatal hemorrhage does its damage, i.e., destroys brain tissue in the initial phase, usually leading to an interruption of the pyramidal tracts in the internal capsule, and therefore to an irreparable complete hemiplegia. Loss of brain function through pressure of the hematoma without serious tissue destruction will generally clear up spontaneously. Removal of blood clots distending the aqueduct and the fourth ventricle and producing a fatal compression of the medulla (Cheyne Stokes breathing and respiratory paralysis) has also been recommended, and occasionally executed with success. Most of these hemorrhages stem from a primary hemorrhage in the basal ganglia. Again, the patient may survive but may remain hemiplegic.

General Treatment. Treatment of increased intracranial pressure is important in all types of strokes, although its mechanism—whether of edema in embolism and thrombosis, or of brain volume increased by a large hematoma—may necessarily vary. In all three, spinal puncture is employed, but its advisability is doubtful except under the conditions described previously. Large encephalomalacias do not profit from the puncture and cerebral hemorrhages may benefit temporarily in the rare instances where there is an accumulation of large amounts of blood within the subarachnoid space. Lowering of the intracranial pressure in hemorrhages may be helped by the deviation of the arterial blood from the head to the abdomen and lower extremities by means of the almost ritualistic use of the ice bag on the elevated head and of hot applications on the abdomen and legs. Another agency is venesection. Almost forgotten in modern medicine, this old and discredited remedy deserves to be tried in plethoric cases of arterial hypertension with facial cyanosis, venous congest-

ion in the neck, and full, pounding pulse. Not more than 300 to 400 cc of blood should be slowly removed and the patient should be closely watched for any alarming symptoms. It must be thoroughly understood that bleeding is definitely contraindicated in encephalomalacia, which again shows the importance of the differential diagnosis. High blood pressure may follow sudden extensive encephalomalacia and this transient reaction must be recognized as such. Care should be taken to protect these patients from all exertion and emotional strain which might raise the blood and intracranial pressure; they should not be moved unnecessarily, should be kept quiet, and should not receive disturbing visitors.

Cerebral edema, particularly that accompanying encephalomalacia may be combated with hypertonic solutions intravenously. From 30 to 50 per cent dextrose or, better, 50 per cent sucrose, solution is usually given in amounts up to 200 cc and more. (A 25 per cent dry serum albumin solution would be better, but it is expensive.) Aminophylline (0.3 to 0.5 gm), which seems to lower the spinal fluid pressure, may be added to the infusion which must be administered slowly (100 cc within about a quarter of an hour). Emptying the bowels with the use of 60 cc of saturated solution of magnesium sulfate helps the process of dehydration.

Support of the cerebral circulation is particularly necessary in arteriosclerotic encephalopathy in cases with poor general circulation and heart failure. Oxygen administration through a nasal catheter aids the general circulation and overcomes anoxia, in itself an important factor in the high mortality rate. Care taken to promote unobstructed pulmonary ventilation serves the same purpose. The patient should be placed on his side to permit free excretion of saliva and to prevent the tongue from falling back. Accumulating mucus should be aspirated through a catheter or with the help of an aspirator.

Against restlessness the different barbiturates are helpful, and, if necessary, may be given intramuscularly or intravenously. Chloral hydrate is an especially good sedative in states of agitation, but has a tendency to lower the blood pressure. It can be given by mouth or rectum in amounts up to 3 gm

daily Narcotics should be avoided for they have a depressing effect on the respiratory center and increase the intracranial pressure

Nutrition becomes a problem when after 2 or 3 days patients are still unconscious or unable to swallow Tube feeding will then be necessary Fluids should be withheld in cases where active dehydration is being attempted but not for longer than 1 or 2 days During the first 3 days 2000 cc of fluid intravenously is usually sufficient Once the paralyzed patient has survived the first week nursing care becomes of decisive importance The skin must be protected against the development of bedsores Much can be done by handling the patient carefully by shifting his weight from time to time by avoiding wrinkles of the bed sheets by using air or better water cushions by inserting cotton rolls or pillows by watching carefully such places as the buttocks heels etc by keeping the patient clean by gently rubbing the skin with 50 per cent alcohol and then powdering it with talcum Both mattress and patient must be protected against urine and feces Diapers absorbent material with oakum special mattresses and urinals have their place Bedsores may be treated with scarlet red ointment (not too long) cod liver oil ointment or balsam of Peru with castor oil in equal parts Deep penetrating skin ulcers may have to be treated surgically with better chances for success now that the local and general use of penicillin has been accepted Hot water bottles must be applied carefully to avoid burns The bowels can be better regulated by enemas (with water containing small amounts of sodium bicarbonate) than with cathartics In case the spontaneous emptying of the bladder is disturbed catheterization at 6 hour intervals under aseptic conditions is necessary

Complete rest should be maintained for about 2 weeks when the period of re education may begin The final outcome of many a severe paralysis depends on how paralyzed extremities have been handled during the many months of slow return of function Regular passive later active movements prevent painful joints and ankylosis and combined with massage they prepare the paralyzed limb for the gradual return of in

nervation Tendency to contractures appears soon and must be counteracted by favoring the very opposite positions e.g. passive dorsiflexion of the foot by means of a wooden board or box flexion of the knee with the help of a pillow support of the extensors of the fingers and wrist and the supinators and adductors of the upper arm Active exercise is often facilitated at least at first in a warm bath which, at the same time has a soothing effect on painful and disturbing spasms These involuntary contractions of muscle groups or of a whole extremity are often difficult to treat Massive sedation may help heat should be tried taking care to avoid skin irritation and occasionally light massage eases them (The use of curare in the form of d-tubocurarine chloride 3 per cent suspension in 48 per cent wax and peanut oil is not without danger) As the patient gradually learns to move his extremities again special attention should be given to the re education of purposeful synergic muscle action such as that needed in walking in reaching for seizing and holding objects in dressing in writing etc The more systematically gymnastic exercises and other forms of physiotherapy are used by hemiplegics the better the results The reader may profitably study the article by E. W. Lowman with its numerous references pertaining to this subject

Contractures which may develop in spite of all precautions and treatment can in selected cases be improved by orthopedic surgery Speech training for aphasic patients necessitates personal experience with the problem and should not be delayed Improvement of paralysis following vascular accidents may continue for 2 to 3 years

Many patients with cerebral arteriosclerosis with or without hypertension—sometimes following strokes but also in the progressive course of cerebral arteriosclerosis toward arteriosclerotic dementia—become therapeutic problems because of their disturbances of sleep restlessness agitation confusion and depression It is generally recognized that the use of barbiturates and bromides does not have desirable effects On the contrary they contribute only too often to increasing confusion disorientation and agitation The different xanthines are more successful here Theobromine calcium sal

icylate (theocalcin), 0.5 gm three times daily, or theophylline ethylenediamine (aminophylline), 0.1 to 0.2 gm three times daily by mouth is recommended. The use of a few cups of strong coffee during the day has often a surprisingly good effect in non hypertensive cerebral arteriosclerosis. Fainting spells particularly when combined with retrograde amnesia and convulsive phenomena usually respond well to dilantin (diphenylhydantoin sodium) although these patients will have to be watched carefully for toxic symptoms. (More information will be found in the article on Epilepsy.) Fainting spells with dizziness or even with true vertigo and then usually combined with tinnitus and diminution of hearing point to ischemic conditions in the vestibular system and the inner ear, possibly on the basis of a sclerosis of the a. auditiva. Such patients may react well to nicotinic acid by mouth in amounts large enough to cause a sensation of warmth in the head. When these attacks of vertigo resemble a Meniere syndrome, papaverine 0.1 gm twice or three times daily (also combined with quinine sulfate 0.1 to 0.2 gm) should be tried. (For more details see under Migraine.)

Dizziness associated with a disturbance of equilibrium pointing to a cerebellar disturbance is often very resistant to treatment. Again, vasodilators, such as nicotinic acid or nicotinamide may be tried. Here, as in other manifestations of cerebral arteriosclerosis, iodine has been used by many experienced physicians, although the rationale of this medication is rather obscure. One may give it by mouth as potassium iodide, 0.3 gm three to five times daily after meals in the form of enteric coated pills. In progressive forms of cerebral arteriosclerosis the administration of sodium iodide intravenously in doses of 2 gm every other day for several weeks, followed by potassium iodide given orally for a few months is recommended. One should watch for signs of iodide intoxication, particularly in patients with hyperthyroid manifestations. Arteriosclerotic parkinsonism is treated in much the same manner as paralysis agitans, hyoscine hydrobromide (0.0005 gm three times daily) being the most frequently used drug. The acute bulbar paralysis on an arteriosclerotic basis often create therapeutic prob-

lems, because of the patient's inability to swallow (dysphagia). Tube feeding as described elsewhere in this book is indicated in these cases.

A general recommendation may conclude this chapter on treatment of cerebral arteriosclerosis. Although this condition should be regarded in general as a progressive disease, leading to irreversible brain tissue damage, everyday experience testifies to the fact that wise management of these patients is often followed by a slowing down or apparent standstill of the disease process over long periods of time. A nihilistic attitude based on therapeutic pessimism is not justifiable except in advanced cases of physical and mental disability.

FREDERICK HILLER

REFERENCES

Ar

- Hamby, W. B. Gross Intracerebral Hematomas. Report of 16 Surgically Treated Cases. *New York State J. Med.* 45:866, 1945.
Lowman, E. W. Rehabilitation of Hemiplegic Patient. *J.A.M.A.*, 137:431, 1948.

1947

- de Takats, G., and Gilbert, N. C. Immediate Treatment of Cerebrovascular Accidents. *Am. Pract.* 2:287, 1948.
Wilson, S. A. K. *Neurology* (Edited by A. Nunan Bruce). Baltimore: William Wood & Company, 1941.
Wolfe, H. G. *Headache and Other Head Pains*. New York: Oxford University Press, 1948.

SUBARACHNOID HEMORRHAGE

To treat successfully a hemorrhage in the subarachnoid space of the brain, one should know the source of the hemorrhage. Evidence of a grossly bloody spinal fluid is common to subarachnoid hemorrhages of different origin. In general one distinguishes between a spontaneous subarachnoid hemorrhage, which some understand to be "non-traumatic," others as "without obvious cause," and a secondary subarachnoid hemor-

rhage, i.e., secondary to a primary intracerebral hemorrhage. It is obvious that such a distinction is, to say the least, unscientific. All of these hemorrhages have a cause, and this should be ascertained, if possible, in each individual case as an essential part of the diagnosis and treatment.

Acute Massive Subarachnoid Hemorrhage Treatment has, up to the present time, remained conservative. Lately, this lack of therapeutic activity has been challenged by neurosurgeons whose criticism (Wechsler and Gross) appears vindicated already by the fact that almost 40 per cent of these patients die in their first attack. The death rate in second attacks climbs up to 70 per cent or more. Spinal puncture has been used in subarachnoid hemorrhage not only as a diagnostic but also as a therapeutic procedure. However, serious doubts are expressed as to the advisability of repeated, even daily, punctures as recommended and practiced. Those who have seen many cases of subarachnoid hemorrhage will agree that the first diagnostic puncture, whereby small amounts, 5 to 10 cc. of bloody fluid are slowly removed, may be followed by a slight, though usually transient amelioration of the general reaction of the brain to the sudden increase of intracranial pressure caused by the bleeding. But there can be no doubt that during the early stages of the hemorrhage, the increased intracranial pressure occasioned by the extravasation frequently has a protective value in tending to reduce the rate of leakage and so promote coagulation. We agree with Symonds when he concludes that "the indications for therapeutic puncture are the signs of a dangerous increase of intracranial pressure, especially if these be progressing." In such circumstances the risk of death from compression outweighs that of the operation itself. Repeated punctures which may easily upset the hydrodynamics in the subarachnoid space and eventually cause a new hemorrhage should be avoided, unless deepening coma, increasing pulse and blood pressure, fresh bleeding and depressed respiration endanger the patient's life.

If, in the presence of an acute subarachnoid hemorrhage, serious doubt exists as to its source and the question of surgical exposure arises, arteriography is indicated.

The use of "iodrast" (iodopyracet) has made angiography a relatively safe procedure, which may be used in the acute as well as in the subacute stages of the hemorrhage (Wechsler and Gross). If, by this means, a vascular malformation or a tumor in an accessible area of the brain, usually over the cortex, is verified, the treatment of choice will be surgical and the neurosurgeon should decide whether or not the tumor should be exposed. If an operation does not seem feasible, roentgen treatment may prevent future hemorrhages.

In cases of acute subarachnoid hemorrhage without a history suggestive of vascular malformation or tumor, and without the suspicion of a pachymeningitis, or of a traumatic, toxic, dyscrasic, or infectious hemorrhage, in other words, in a case of most probable aneurysmal subarachnoid hemorrhage, arteriography for localization of the aneurysm and for possible surgical management of the case must be considered by the responsible physician. Whether one decides on an arteriogram or not depends, first, on what one has decided to do in case an aneurysm is found, and, second, on the patient's condition (continued bleeding, deepening coma, etc.), and also on whether one is dealing with a first or with a repeated hemorrhage.

An arteriogram for the visualization of the aneurysm is indicated in cases which enter the hospital in a second or in an even more frequently repeated attack. These patients have only half as good a chance to survive as those suffering from a first hemorrhage. An arteriogram is also desirable in cases, even without repeated hemorrhages, which show neurologic signs of increasing local pressure, probably due to an enlarging aneurysm.

The surgical treatment of aneurysm, as performed by Dandy and others, shows by its high mortality rate (over 50 per cent) that, at least with the present technique, it cannot be recommended generally in first attacks of subarachnoid hemorrhage, with the possible exception of cases which show the ominous signs of continued or repeated bleeding.

Ligation of the common carotid which reduces the blood circulation of the ipsilateral side of the brain about 50 per cent

and is less dangerous than ligation of the internal carotid will certainly not cure an aneurysm at the base of the brain but it may stop the bleeding and favor the thrombotic occlusion of a ruptured aneurysmal sac. It will not have any marked effect on the tumor signs of an aneurysm. Its usefulness is well established in arteriovenous aneurysms with pulsating exophthalmos which he outside our discussion and it may be recommended in acute subarachnoid hemorrhage particularly when the first hemorrhage threatens the patient's life or in any case of repeated hemorrhage in younger individuals. Wechsler and Gross do not see any danger in this procedure although the American and European literature contains reports of usually transient hemiplegias and brain damage demonstrated in ventriculograms after common carotid ligation. Ligation has the advantage over direct surgical approach in aneurysm in that it is technically simple and its risks are slight compared with those of the other operation. The ligation must of course be preceded by an arteriogram in order to ascertain the site of the bleeding branch of the internal carotid.

Operative procedures present a still more difficult problem when patients ask advice one or more months after the acute signs of a subarachnoid hemorrhage have subsided. Here H. G. Wolff's suggestion can be accepted that arteriograms should be made in the presence of significant symptoms referable to a probable aneurysm such as motility and sensory disturbances pointing to a localized intracranial mass. Yet we think craniotomy and even ligation of the common carotid should depend on the clinical course. One should not be too pessimistic as to the danger of brain tissue damage (hemiparesis, aphasia, mental disturbances, etc.) once the patient has survived his first acute attack. In most instances these conditions improve gradually and often leave only small functional defects. One will be more reluctant in recommending a carotid ligation on the left side (in a right handed person) than on the right and one should always consider the general brain condition which does not always correspond to the age of the patient.

GENERAL MANAGEMENT. The general management of an acute subarachnoid hemor-

rhage often has to deal with considerable agitation, restlessness and excitement in the patient a condition that is anything but conducive to cessation of the bleeding. Paraldehyde 30 to 60 cc per rectum, barbiturates, intramuscularly or intravenously (e.g. sodium amytal 0.3 to 0.5 gm) will usually quiet the patient. If headaches or pain along the spine (and sometimes also in the lower extremities) make the patient suffer and contribute to his restlessness, codeine sulfate (0.06 gm) or demerol (100 mg) subcutaneously is recommended. Morphine in the presence of cerebral respiratory impairment is dangerous. Magnesium sulfate 300 cc of 25 per cent may be given by Murphy drip at a rate of 1 drop per second. Increased intracranial pressure may be counteracted by the intravenous infusion of hypertonic solutions. In addition the rules of conscientious nursing care should be followed as outlined in the treatment of apoplexia. Patients should be kept in bed 4 to 6 weeks after the bleeding has ceased.

As to the further medical supervision of these patients particular attention should be given to any disturbances of cerebral function and to the blood pressure. In a large series of cases of subarachnoid hemorrhage reported by W. B. Hamby and others arterial hypertension was "the only constitutional disorder that occurred with sufficient frequency to be regarded as more than incidental." From such observations as well as from the prevalence of migraine in these patients one may conclude that patients who have suffered a subarachnoid hemorrhage should be checked and treated for abnormal variations of blood pressure and that their way of living ought to be so well regulated as to protect them against headache which because of a concomitant dilatation and distention of the intracranial arteries may precipitate new hemorrhages.

The treatment of subarachnoid hemorrhage of other etiologies must rest first of all on the approach to the underlying pathology. It will be surgical in the presence of certain traumatic types such as primary subdural hematomas and hemorrhagic pachymeningitis. It will be medical in the various types of blood diseases and dyscrasias as well as in infectious or toxic conditions.

FREDERICK HILLEN

REFERENCES

- Courville C H *Pathology of the Central Nervous System: a Study Based upon a Survey of Lesions Found in a Series of 15,000 Autopsies* Mountain View Calif California Press Publishing Assoc a tion 1945
- Dandy W E *Intracranial Arterial Aneurysms* Ithaca N Y Comstock Publishing Company 1944
- Ramby W H *Spontaneous Subarachnoid Hemorrhage of Aneurysmal Origin: Factors Influencing Progress* JAMA 136 520 1948
- Symonds C P *Spontaneous Subarachnoid Hemorrhage* Quart J Med 18 93 1954
- Wechsler I S and Gross W W *Cerebral Arteriography in Subarachnoid Hemorrhage* JAMA 136 517 1948
- Wolff H G *Headache and Other Head Pain* New York Oxford University Press 1943

HEADACHE

The physician who has to treat a patient suffering from headaches especially those of a chronic recurrent or alarming type is confronted with the necessity of understanding the etiology or the mechanism of the headache in question. Harold G. Wolff's work *Headache and Other Head Pain* the first systematic approach to clarification of the pathophysiology of the various types of headache is recommended to all those who desire a more detailed account than this chapter can give them.

Migraine The classical attacks of migraine headaches characterized by their periodic occurrence usually but not always by their unilateral frontotemporal distribution their prodromal sensations and cerebral manifestations are generally explained as the result of primary intracranial and extracranial vasospasms followed by the painful dilatation and distention of branches of the external carotid artery. The premonitory sensations due to vasospasm are for the most part visual such as scintillations scotomas and hemianopsias but they may also include both sensory and motor disturbances of hemilateral distribution and speech disorders. Like epilepsy to which it has some relation (Lennox) migraine may betray itself in equivalent periodic emotional or mood disturbances and even mild twilight states. Or with or without headache it may exhibit somatic phenomena of a painful character in different parts of the body and extremities

as well as nonpainful intestinal disturbances metabolic upsets water retention fever etc. All migrainous phenomena varying from case to case can be linked to different causative or merely precipitating factors which like allergies endocrine activities or disorders and frequently psychogenic or personality disturbances have to be well understood.

The treatment of migraine though mostly concerned with the headache will be the more successful if the pathogenetic peculiarities of the individual case are understood and if therapy of the painful distention of extracranial or meningeal arteries is then supplemented by consideration of the pre-headache phase and of the underlying causes.

The simplest way to relieve or even stop the usual temporal headache is to reduce the blood flow into the distended palpably pulsating arteries by digital compression. A few patients feel immediate relief with pressure on the temple others with pressure on the common carotid. A tight wide rubber band around the head cold compresses and any other measures which will diminish blood flow are of value as well as procedures to lower general arterial pressure such as a warm bath followed by bed rest.

If given early enough ergotamine tartrate in use for more than 20 years has proved to be effective in the majority of migrainous headaches. However it is of practically no value if the headache has lasted for many hours and if organic though reversible edematous thickening of the palpable arteries has taken place. But if given early and in a sufficient dosage its damping effect on the excessive pulsation of the extracranial arteries as the temporal artery for instance is visible and the headaches often subside with

is desired the same dose may be administered intravenously. As an alternative ergotamine by mouth taken sublingually is recommended. As soon as possible after the beginning of the headache a dose of 3 to 4

should remain under the control of the

physician and should not be given more often than once a week. Furthermore undiagnosed hypertension and cardiovascular disease must be regarded as contraindications to this treatment. Should the patient show hypersensitivity to ergotamine, such as nausea, vomiting, paresthesias, muscle and chest pain and prostration lasting for more than 24 hours, further use of the drug may be hazardous. As an antidote, atropine sulfate 0.5 mg subcutaneously or calcium gluconate 10 cc intravenously may be given.

If ergotamine is contraindicated or must be discontinued, other drugs that will produce arterial constriction may be tried. Dihydroergotamine is less toxic than ergotamine and may be given in 2 to 4 mg doses intramuscularly (Horton). Ergobasine tartrate or ergotrate (0.2 mg intramuscularly) is not as effective as ergotamine. Ephedrine, benzedrine and pituitrin are either less effective or produce undesirable concomitant reactions. Only caffeine as caffeine sodium benzoate 0.3 to 1.0 gm or as black coffee offers help without unpleasant side effects. It may also be given in smaller doses combined with ergotamine (1 mg of ergotamine to 100 mg of caffeine, 2 tablets at the onset of a migraine attack) as originally recommended by B. T. Horton. Combined with analgesics and sedatives, caffeine has been used against migraine for many years. The benefit of octin (Palmer) appears to be doubtful.

It should be understood that when given in amounts high enough to raise the systemic arterial pressure, this first group of remedies will fail to show beneficial effect. This must be kept in mind particularly when ephedrine or caffeine is used.

Histamine for the treatment of migraine has been employed intravenously by Butler and Thomas and both intravenously and subcutaneously by Horton and Macy, who prefer the latter method. The doses to be given will be described later in the section on Histamine Headache. It seems rather characteristic that Horton and his co-workers should find a greater percentage of significant improvement in patients with atypical migraine than in those with the typical variety. Although more than 75 per cent of all patients treated showed a significant improvement during the period of treatment, practically every patient experienced a recurrence

of migrainous attacks when histamine therapy was decreased below an individual critical level or was stopped entirely.

The beneficial use of histamine in migraine appears surprising in a condition where vascular hypotonicity and increased pulsation are already present and causing pain. The explanation suggests itself that any amount of histamine or for that matter amyl nitrite, acetylcholine and similar drugs, large enough to cause a drop in blood pressure will diminish or even stop the transient migrainous headache which, once the blood pressure has regained its initial level, will be replaced by a headache of mixed origin due to relaxation of both intracranial and extracranial arteries. The better results gained by constant subcutaneous sublingual doses of histamine are obviously much more of a preventive than a curative character.

Analgesics and narcotics are the most frequently used drugs against migraine, their common characteristic being to raise the threshold to pain. In measuring the effect of these various drugs, H. G. Wolff has found that 0.3 gm acetylsalicylic acid equals 0.3 gm acetophenetidin. Both elevate the pain threshold 20 to 25 per cent for about 14 hours; larger amounts (1 to 2 gm) for from 2 to 24 hours. Pyramidon (aminopyrine) 0.3 gm with or without caffeine 0.15 gm given several times a day often alleviates the pain but presents the danger of possible agranulocytosis. Antipyrine (phenazone) 0.3 gm is also frequently used although it is even more poisonous than acetanilid and phenacetin. It seems reasonable therefore to give preference to the relatively harmless acetylsalicylic acid which, particularly when taken with an alkali, will cause hardly any undesirable reactions. Where analgesics prove to be ineffective, codeine phosphate 0.03 gm will often be helpful, particularly in migrainous attacks with violent nausea and vomiting. Here the subcutaneous route is preferable.

The older, especially the older French literature contains so many observations pertaining to the close relationship between migraine and gout that provided such a coincidence is established in a given case, an appropriate treatment may be tried.

The treatment of a status migrainosus may be difficult because of the unfavorable emo-

tonal excitation apprehension and depression with which so many patients react to the extremely wretched and miserable condition that may last uninterruptedly for days As is generally known the drugs usually given for migraine even ergotamine used intravenously have but a short and unsatisfactory effect on the patient's misery Codeine 0.1 gm subcutaneously is often necessary and may have to be administered repeatedly Morphine with its danger of addiction should be prescribed only exceptionally and not a few patients experience increased nausea and vomiting after taking it Demerol

in a darkened room and given cracked ice by mouth in order to counteract the nausea and vomiting The stomach is better kept empty and fluids if necessary may be given intravenously hot

very rarely the physician's greatest diligence and the best nursing care is often most successfully treated by intravenous "anesthesia" Sodium amytal 0.5 gm and if necessary

usually will if absolutely necessary prolong the sleep sufficiently to help the patient over his attack The rare cases of status migrainosus with papilledema (indicative of brain swelling) demand intravenous infusion of hypertonic (sucrose or albumin) solutions

Occasionally a patient finds that once some treatment has cut short his premonitory symptoms the usual headache will be aborted For treatment of this pre headache phase of migraine many different vasodilating drugs have been used The good results of daily subcutaneous treatment with histamine in certain cases has been already mentioned However continuous histamine injection treatment of an illness which ordinarily has remissions of weeks and even months does not appear ideal The reader will find himself more confused than informed by the many claims of this or that substance offering the abortive treatment of a migraine attack Both O_2 and CO_2 have been acclaimed and it is true that they may occasionally help but it

is equally true that their action is unpredictable The well known vasodilators such as sodium nitrite and glyceryl trinitrate though effective in doses of 0.05 gm and 0.0005 gm respectively may help to abolish the symptoms of vasoconstriction but they may also precipitate the headache phase The simplicity of the procedure recommends the use of amyl nitrite in perles which inhaled from a handkerchief may abort an attack (but so may a glass of brandy or whisky) Nicotinic acid (niacin) may be taken in tablets as a vasodilator over long periods of time Atkinson prefers the combined peroral and parenteral administration of 50 to 100 mg In cases with severe cerebral angiospastic phenomena (such as hemianopsia or hemilateral motor or sensory disturbances) the intravenous injection of approximately 100 mg of the niacin or 30 mg of the amide is more reliable than when given by other means The number of drugs used for the same purpose is considerable The xanthines meclocholyl doryl and many other antispasmodics have proved to be helpful in individual cases only to fail when tried on a larger group Papaverine should be given intravenously in a dose of about 0.1 to 0.2 gm Many physicians prefer the use of sedatives which like phenobarbital (0.05 gm three times daily) can be taken for long periods and can raise the threshold of visceral response The bromides also are used for the same purpose There is little doubt that regular sedation acts primarily on the general rate of emotional tension and nervousness an important factor in the precipitation of

cerebral arteries is uncertain and it is too dangerous a drug to be used for preventive purposes over a long period of time

In a disorder like migraine where our

nervous tension poor adjustment neurotic solutions of conflicts morbid attitudes anxiety etc plays an important role in the management of patients with migraine and it appears probable that not only sedatives

but any long utilized regimen and medication are often successful, less because of any specific effect than because of the reassurance and confidence derived by the patient from such a treatment. The importance of psychotherapy in migraine cannot be overstressed. As long as it does not demand great experience and special technique, psychologic treatment can well be left to the general practitioner and internist. The first rule is genuine and personal interest in the patient's problems. Personal acquaintance with the patient's family, his environment, type of work, and hobbies places many a practitioner in a good position to understand the case. The

tioner will find a clear and understandable analysis of the various personality problems and difficulties of these patients, and also good advice on how to treat them. A neuro-psychiatrist should be consulted where nervousness, sense of failure, fear, frustration in security, aggressiveness, etc., are conditioned less by existing or known circumstances than by the manifestation of a defective nervous, neurotic personality with long history of nervous symptoms.

The importance of allergy in migraine has been considered for many years (Bassoe Best and Taylor, J. W. Scott), and parallels have been drawn to the mechanism of asthma and migraine. To support such a concept, the effect of infections on migraine and the occasional eosinophilia of the blood have been pointed out. Certain foods may precipitate attacks in predisposed persons. Thus it appears reasonable that allergy studies should be made in migraine patients, particularly in the face of other evidence, e.g., urticaria of an allergic condition. Often chocolate is found to serve as an antigen in persons afflicted with headaches. The evidence of histamine sensitivity in itself does not prove an allergic condition, although excessive amounts of histamine are produced in allergic reactions and may precipitate headaches by vasodilatation. Antihistaminic treatment is discussed under Histamine

by desensitization. As a nonspecific treatment the intravenous injection of from 0.5 to 2.0 cc of a 5 per cent solution of peptone may be tried. These injections are given twice weekly at first and then continued at lessened frequency until finally one injection per month is given. Before a migraine attack gets under way, the use of calcium lactate or

ever it cannot be denied that many headaches, including migraine, are precipitated by an intestinal disturbance, especially by constipation, a condition which should be eliminated in every migraine patient.

Endocrine disturbance or fluctuations at least as conditioning factors, appear often in the history of migraine. The peculiar relationship of spells to menstruation, pregnancy, and the menopause seems to support such a concept. Yet, in reality, a change in the patient's activities and attitudes may be more important than the endocrine element. Treatment of migraine with pituitary preparations, theelin, amniotin, estrogens and gonadotropic hormones must always depend on a sound indication, i.e., on the evidence of a definite hormonal disorder. A thorough study of the patient's endocrine status may

treating migraine related to the menstrual period and that suffered by individuals of the so-called Lorain-Levy pituitary type. He used placental estrogenic substance 2 teaspoonfuls a day, increased to 4 a day before menstruation. He relieved migraine occurring during the menopause by the use of alpha estradiol benzoate. Patients with hypothyroidism and with basal metabolic rates of -20 or more per cent were benefited by thyroid medication, while the hypopituitary types improved with pituitary extract. S. A. Kinnier Wilson has followed the rule of administering thyroid extract in small doses (seldom exceeding 0.12 gm. night and morning) with a view of maintaining sympathetic tonus, and has had "impressive results." Treatment of

is not rare and can be treated relatively easily

women with migraine by means of hysterectomy, oophorectomy, and radium sterilization does not guarantee a cure and is not to be advised (Alvarez)

Other methods of treating migraine have been directed, with various results, against disturbed liver function although there is no proof that such a disturbance plays a significant role in migraine. Among other remedies, the use of decholin or sodium glycocholate has been advocated. In order to overcome hepatic malfunction, Ivy and his co workers have used chondroitin sulfuric acid, a substance employed by the liver in detoxifying processes. Capsules of 2 to 3 gm were given daily by mouth after meals for periods of many months, and, as long as this treatment continued, relief from migraine was observed. Drewyer has reported equally good results in 67 per cent of his cases. Occasionally, we, too, have seen good results.

In the surgical treatment of migraine, the injection of a small amount of a 1 to 2 per cent solution of procaine hydrochloride around the temporal or frontal arteries is a simple procedure and may bring prompt relief from an acute attack. Ligation of the temporal artery or resection of a small piece may prolong the "cure" for many months, but this should be done only in cases which do not respond to medical (or possibly psychiatric) treatment. Some patients, whose pain is not relieved by ligation of the temporal artery but continues in a rather unusual distribution (in the face, below the eye, in the jaws, neck, and shoulder), may be relieved by ligation of the middle meningeal artery (von Storch). This operation was combined by Adson with removal of the superior sympathetic ganglion, cervicothoracic sympathetic ganglionectomy, and trunk resection—an operation which appears almost as excessive as the subtemporal decompression proposed for inveterate cases. Instead one may try, in desperate cases, an alcohol injection of the gasserian ganglion or a partial resection of the trigeminal roots, leading to an analgesia over the forehead, front and temple, and to freedom from headache. The danger is the occurrence of trophic lesions of the anesthetized cornea. Obviously, good results can be expected only when the spread of pain is limited to that portion of the head innervated by the fifth

nerve. Only rare and well selected cases should be chosen for this operation.

The attending physician should be aware

usual types of trigeminal neuralgia, or from Sluder's neuralgia (attributed to infection of the sphenoid and posterior ethmoid sinuses affecting the sphenopalatine ganglion). These cases should be subjected to a treatment for migraine, especially to cold applications and ergotamine injections, before the

The this I G Wolff, would prove that the pain is due to dilatation, distention, and abnormal pulsations of the internal maxillary artery and its branches.

Migrainous headaches in hypertension are discussed elsewhere.

Painful muscular contractions about the head and particularly about the neck complicate many cases of migraine. They may be due to the same vascular dilatation and distention as those observed in the temporal artery, but the fact that these neuralgic pains usually persist between the migraine attacks and as a rule do not react to ergotamine, as well as the sensitivity of the muscles to pressure, characterizes them as muscular pains. As such they are nonspecific and occur in the presence of many kinds of extracranial and intracranial abnormalities, but may also occur as the expression of emotional tension. They respond to psychotherapy and often to physiotherapeutic management (see below).

Headaches after Skull Trauma. Headaches associated with or following injuries of the head are of various types, the appropriate treatment depending on the nature of the damage incurred. In injuries of the skull, the local pain and tenderness is a pain and not a true headache, and its duration is usually short unless there is a localized injury to a nerve branch, severe scarring, adhesions, etc. In such cases the injection of a few cubic centimeters of 1 per cent procaine solution, or even the excision of the painful scar seems indicated.

It is only too well known that many individuals with head injuries complain not only of local tenderness at the site of the injury,

but of aches and pains about the head. The majority of headaches after trauma consist of pressure sensations, a feeling of weight and tightness, aching pain with cap like distribution, painful pressure sensations over the vertex, at the base of the skull, over the eyes, associated with local tenderness, and occasionally dependent on certain positions and movements of the head. These aches can be accompanied by giddiness, unsteadiness and dizziness. The question as to the nature of such headaches and therefore also as to their treatment, is often difficult to answer. There is no conclusive relationship between either skull fracture or the neurologic findings and these headaches, although dizziness, which after all is but another subjective symptom, accompanies them rather frequently. The presence of painful meningeal injury and subsequent scarring has to be thought of. In severe post traumatic headaches a spinal puncture may give valuable information and even a pneumocephalogram may be indicated if such headaches last longer than about 3 months. Either procedure by itself, and not always for understandable reasons, may put an end to the patient's complaints.

F
tion
or
ment, may cause severe intracranial head aches. study
would and
could e least
indicate the right treatment for such a condition. It is evident that acute accumulation of blood in the epidural and subdural as well as in the subarachnoid spaces causes headache, and thus chiefly through displacement and traction on pain sensitive intracranial structures. This headache resembles a tumor headache and usually disappears with the removal of an epidural or subdural hematoma (or cyst) and the spontaneous resorption of blood in the subarachnoid space.

Like other post traumatic nervous phenomena, lasting headaches have been regarded as proof of increase of vascular sensitivity following trauma" (Friedman and Brenner), and have been likened to histamine headaches. Painful pal and cerebral arterial dilatation (similar to the histamine effect) combined with various dilatation and

traction pains may be justly assumed in post traumatic headaches with abnormally low spinal fluid pressure. In such cases, where the liquor production is probably diminished, a horizontal position, or perhaps merely bending of the head, may give relief, but the headaches will be abolished promptly by hypotonic saline solution intravenously (200 cc of a 0.4 per cent solution), and even more promptly by the restoration of the intracranial pressure to its normal level by intrathecal injection of normal saline solution.

In many instances lasting post traumatic headaches are muscular contraction pains about the cranium, of the same type that occurs in migraine, and may result reflexly from all kinds of noxious impulses. They may indicate a sustained postural muscle contraction as an expression of emotional tension, fears, etc. The presence of localized pressure pain, usually in the back of the head and neck, the temples and elsewhere, makes one think of traumatic myositis (see below), fibrositis, or periostitis, a diagnosis difficult to prove and probably much rarer than the painful reactive muscular contraction. Treatment of a circumscribed, painful muscular contraction can be accomplished by injecting about 10 cc of a 1 per cent procaine hydrochloride solution in the muscle. One must be careful not to put such an injection close to the atlas. If successful these injections can be repeated at 2 or 3 day intervals. Hot applications are useful in treating these painful muscle contractions, and one can make use of the radiating heat of infra red lamps or the moist heat of hot packs which most patients prefer. The heat should be applied at the site of the contraction, morning and night, and immediately for muscle

tional or organic induration in a muscle. Mild friction, gentle kneading, and slight vibration not painful to the patient are employed. The pressure should be gradually increased and a gentle stroking massage should terminate each treatment. If this therapy is well performed the patient should be relieved from his aches after each daily massage. Stretching of the muscles, as well

as "pricking with a needle," is also recommended, but will only rarely show a result superior to that of heat and massage. Acetyl salicylic acid and mild sedation, such as

often benefit from sedation. The emotional factor contributing to this kind of headache is usually obvious in the general tense and nervous attitude of these patients, and can be demonstrated by the frequently excellent, though transient, effect of sodium amytal, 0.5 gm intravenously. Psychotherapy in one form or another will usually help the physiotherapeutic management.

The high incidence of long lasting headaches after skull injuries, which in themselves can hardly explain the type and duration of the pain, calls for a possible prevention of post-traumatic headaches. Brenner and his co-workers have found that the incidence of headaches after industrial accidents is suggestively higher than that following recreational and domestic accidents. They also found a high incidence of psychoneurotic manifestations prior to the accident in patients whose post-traumatic headaches lasted for more than 2 months after injury. There is also a high incidence of chronic post-traumatic headaches in individuals who, either immediately after the accident or later, show pronounced emotional reactions and mood disturbances, such as hypochondriasis, anxiety, irritability, apprehension, and difficulties in concentration, as well as great fatigability. Unfavorable life situations, especially occupational difficulties and pending litigation, have a pronounced effect on post-traumatic headaches. H. G. Wolff found that almost three quarters of these patients had anxiety conflicts and that about four-fifths were actually psychoneurotic before they suffered head injury. Conflicts concerning compensation play an important role in at least sustaining many post-traumatic headaches. Wolff cites the excellent therapeutic effect of an "accelerated convalescence" observed by many during World War II. No doubt many post-traumatic chronic headaches are "iatrogenic," i.e., induced by the overcareful and anxious attitude and orders of the attending physician. Many such headaches may be avoided

by limiting bed rest following skull injury to the minimal necessary period, after ascertaining the absence of intracranial damage. This does not preclude medical supervision as long as organic complications, such as a subdural hemorrhage, are to be reckoned with. Only too often the patient's fears of brain injury with anticipatory disturbances to follow reflect merely the physician's overcarefulness. The patient should be put at ease and reassured that no untoward after-effects of his injury are to be expected. Patients who complain of post-traumatic headaches which, like painful muscular contractions or migraine-like headaches, betray a state of emotional tension, will derive relief and general benefit when, with the help of their physician, they learn to understand the true nature of their condition. Neurotic maladjustment of longer duration will necessitate treatment by a psychiatrist. Of decisive importance is the prompt and definite settlement of compensation claims for injuries. Many a post-traumatic headache disappears automatically when a final settlement is reached and the patient can direct his hopes and energy to constructive ideas about his life and work, and is freed from feelings of frustration, resentment and anxiety which may dominate him as long as he is fighting for what he feels are well founded claims.

Referred Pain in the Presence of Pathology of the Nose, Ear, Eyes, and Teeth. Painful conditions of this type may assume the character of a true headache, but more often they are described as an aching pain radiating to this or that part of the head, face, or neck. Their treatment depends primarily, of course, on a correct diagnosis and then coincides with treatment of the basic trouble.

Headaches and pain of nasal and para-nasal sinus origin are usually due to the inflammation and engorgement of the turbinates, the ostia, the nasofrontal ducts, and the superior nasal structures. This pain is felt as a referred headache in specific parts of the head, usually in the front (between the eyes), or over the vertex, when the superior nasal structures are involved, and in the temples combined with pain in the jaws, teeth, and the zygoma region, when the middle or inferior nasal structures are the site of the swelling and irritation.

Treatment of this headache and pain is directed primarily against the swelling of the nasal mucous membrane. Solutions of cocaine (0.2 per cent), procaine (2.0 per cent), neosynephrine (1.0 per cent), or privity (0.1 per cent) are employed locally. The use of the benzedrine (amphetamine) in haler benefits many patients, but appears to be not without danger in coronary disease. Ephedrine sulfate preferably as a sterilized 1 per cent solution in 0.9 per cent saline, produces prompt shrinkage and can be used as a spray or nose drops. These drugs may be combined with local chemotherapy and with any kind of treatment directed against the nasal condition. The usefulness of hot packs and steam in headaches caused by inflammatory conditions in the nose and sinus cannot be overemphasized. Acetyl salicylic acid 0.5 gm., given repeatedly, aids the good effect of heat. Only more serious underlying conditions such as perostitis, osteomyelitis, and epidural inflammation necessitate the use of codeine or morphine. Here also we mention the surgical treatment of organic nasal obstructions (septal deviations and polyposis), which, particularly in combination with vasomotor changes in the mucous membranes, can be the cause of headache.

Headache originating in the ear often occurs as referred pain in different parts of the head because the nerve supply is so diverse (the fifth, seventh, ninth, and tenth nerves, as well as the upper cervical roots for the scalp and muscles in the vicinity of the ear). For the most part pain in the ear and pain referred from the ear occur in destructive or inflammatory ear disease and are often combined with painful contractions of the neck muscles leading to a tilting of the head to the diseased side. Periostritis and inflammation of the dura (extradural abscess) cause local pain and tenderness as well as more diffuse headache, over and behind the ear. Treatment corresponds to that mentioned in the foregoing section, and is, of course, primarily an otologic problem. However, it should be remembered that pains in the ear and headaches around the ear may occur also as referred pain in the presence of disease in other parts of the head and neck, e.g., the nasopharynx, larynx, teeth, temporomandibular joint, and upper

cervical spine. Neuralgia of the fifth and ninth nerves, and particularly of the geniculate ganglion (Hunt's syndrome) includes ear pain as a more or less characteristic symptom.

Headache apparently originating in the eye is often treated as ophthalmic, not always on sufficient evidence and therefore often unsuccessfully. Wolff has concluded that pain from increase in intraocular pressure radiates to the entire distribution of the ophthalmic branch of the fifth nerve and may be accompanied by nausea. Only traction of the extraocular muscles and of the iris is painful. Artificially induced hyperopia and astigmatism (but not myopia) cause headache. Cushman found that refractive errors present for many years seldom cause headaches unless additional factors, such as overexertion, overuse of the eyes, psychic disturbances, and other illnesses enter into play. This observation is borne out by the fact that it is usually long-lasting eyestrain (caused by reading etc., particularly in poor light) that, in persons suffering from hyperopia, astigmatism or muscle imbalance, causes frontal or occipital headache. Many of these patients are aware of eyestrain and, in addition, complain of unpleasant sensations within the eyes and of eye fatigue (Heterophoria or muscle imbalance can be assumed when the closing of one eye eliminates the headache). Treatment consists in correction of whatever physical disturbance has been established.

The intense pain in glaucoma is usually worse in the early morning and is often accompanied by increasing headache with occasional nausea and vomiting. Pressure on the eyeball intensifies the headache, and

a solution intravenously may be given additionally.

Intraocular inflammation causes ache around the eye and the temporal region, as well as intraocular pain and photophobia. A 1 per cent atropine solution in the conjunctival sac usually helps to relieve the headache and pain, but codeine and morphine injections may be necessary. The treatment of headaches which may be associated with inflammation of the cornea, conjunc-

tiva, or the optic nerve = part of the specific therapy of these conditions

Headaches associated with toothache and also those which sometimes follow dental extraction, are rather infrequent. In acute cases the radiation of pain from the source of infection, i.e., from the decayed tooth or from the tooth socket, is usually obvious and disappears with elimination of the source. Electric stimulation of such a tooth will aggravate or precipitate pain and headache. In doubtful cases, local anesthesia around a suspected tooth will abolish irradiating pain and ache if the condition of the tooth is the cause of the distress. Treatment of such headaches should be directed primarily against the source of pain and headache.

Occasionally one finds *disease of the temporomandibular joint* as the cause of headaches. Costen has described this syndrome in which the headache is usually localized in the supra orbital and temporal region, but can spread to the vertex and occiput. The displaced condyle of the mandible may also cause tinnitus and other unpleasant sensations in the ear as well as impairment of hearing. Disturbance of saliva secretion is a frequent concomitant. This malocclusion headache is often promptly relieved by interposing a flat object between the jaws and by correction of the overclosure.

Occipital headaches and pains irradiating down into the neck and shoulders may accompany any of the painful conditions described in nose, ear, eyes, and teeth but are caused by muscle contraction. Their functional nature and their treatment have been previously considered.

Headaches from Cervical Myositis Myositis is supposed to be one of the most frequent causes of headache. In a number of patients the diagnosis of infectious myositis is probably correct, although there is no histologic proof of such a condition. Distress is usually felt as a deep ache or pain in the neck and occipital region, sometimes localized in the skull itself. Any movement of the neck, particularly after the head has been kept in the same position for some time, as after a night's rest, initiates or aggravates the pain. Even slight manual pressure on the scalp of the occiput and on the neck muscles is painful. The pain is steady and may be associated with nausea, dizziness, and some-

times anorexia. It may irradiate to other parts of the head or down the neck toward the shoulders. The palpating finger usually detects extremely painful, indurated nodules in the scalp and in the involved musculature. This rheumatic headache (so named by Osler) is distinguished from muscular contraction headache (described above as the effect of emotional tension) only by the circumstances, e.g., general or local infection, toxic conditions, effect of cold, drafts, etc., which characterize the clinical picture of myositis. Not so rarely disease of the cervical spine, usually arthritic but sometimes traumatic, may be the cause of "rheumatic" suboccipital and neck pain and headache. The correct diagnosis will indicate the appropriate treatment.

The treatment of true myositic headaches corresponds to that outlined in the section on Post-traumatic Headaches. In severe cases immobilization of the neck and support by a collar, as well as liberal use of acetylsalicylic acid is recommended. The local infiltration of the painful muscle with 10 to 20 cc of 1 per cent solution of procaine hydrochloride may be tried in cases which do not respond to local heat, massage, and "anti-rheumatic" liniments. The therapeutic procedures used in fibrositis in general should also be applied in rheumatic headache. Cases which do not respond to such treatment within a few months, and cases where bone disease or a focal or general infectious condition as well as some other primary headache are ruled out, should always be suspected of being "tension" headaches and be subjected to a psychologic approach.

Headaches in Temporal Arteritis. Temporal arteritis was only recently described by Horton, Magath, and Brown. The painful-

sometimes also localized in the jaw and teeth, zygoma, ear, and occiput—all this in a patient, usually past 60, suffering from a fever and complaining of malaise, anorexia, and weight loss, distinguishes this condition from headaches due to other intracranial or extracranial sources. Unlike periarthritis nodosa and disseminated lupus, with which temporal arteritis has certain histologic find-

ings in common, the temporal "arteritis" is usually restricted to the arteries of the head (H G Wolff therefore recommends the term "cranial arteritis") and is limited in duration. Inflammation of the central retinal artery and of brain arteries may complicate the picture. Treatment of these headaches and pain is purely symptomatic, although an attempt to control the underlying infection with antibiotics, etc., should be made.

Headaches after Spinal Puncture. Headache here results from the drainage of large amounts of spinal fluid or from postpuncture leakage. Not every patient complains of such headaches after lumbar puncture, and one may see sequelae more frequently in patients who show no evidence of brain pathology. The headache is dull or throbbing, sometimes more suboccipital, sometimes more frontotemporal.

Treatment aims at a restoration of the ratio of brain volume to spinal fluid volume. The volume of the spinal fluid may be restored to normal by replacing the amount of fluid withdrawn by physiologic saline solution, but such a procedure will not prevent further leakage. Only the use of a fine puncture needle will help prevent this undesirable complication. The intravenous administration of hypotonic solutions, e.g., 50 cc of 0.225 per cent saline, as recommended by Reese and Shulak, or a greater quantity of a less hypotonic solution, may abolish the headache. Inhalation of amyl nitrite, which augments the brain volume by arterial dilatation, may be tried, but its success is rather unpredictable. The best treatment still is to keep the patient in bed with his head lowered and possibly lying on his stomach during the first 24 hours after puncture. Bed rest should be extended as long as the upright position causes recurrence of headache. Oversensitive patients may develop postpuncture sequelae of a purely functional type, especially occipital headaches due to muscular contractions, particularly in the suboccipital neck region (see above). The administration of salicylates, mild sedatives, or 0.05 gm codeine, immediately after the puncture will help to prevent such reactions. The suboccipital puncture of the cisterna magna avoids postpuncture headache, but this procedure, though not at all difficult, should be reserved for those physicians who

have had considerable experience with the method. True meningitic reactions, including severe headache after spinal puncture and originating in an aseptic meningitis, are rare, and usually disappear spontaneously without specific treatment.

Histamine Headache and Headache in Infections and Toxic States. B T. Horton has called attention to a peculiar type of headache which he first called erythromelalgia of the head, then histamine cephalalgia, and which, according to him, resembles headache induced by injection of histamine. This type of headache is of short duration, is not accompanied by premonitory symptoms, and may strike a patient several times within 24 hours. Also, it may awaken him several times during the night. It may disappear after the victim arises, only to return when he again falls asleep. The headache is paroxysmal, chiefly frontotemporal, but occasionally occipital, and is accompanied by nasal congestion, flushing, increased perspiration of the affected side, and lacrimation. Attacks come in cycles, to be followed by long or short intervals completely free of pain.

A true histamine headache is an intracranial arterial syndrome, while migraine is a predominantly extracranial one. It would seem that the lack of response to ergotamine in the case of the true histamine headache would be a simple means of distinguishing Horton's cephalalgia, produced by a dilatation and distention of pial and cerebral arteries under the effect of histamine, from a typical or atypical migraine, caused by a painful distention of branches of the external carotid artery.

Experimental and clinical evidence shows that the headaches so frequently complained of by patients with influenza, brucellosis, typhoid fever, sepsis, malaria, typhus, etc., and those occurring after different vaccinations and injections of foreign proteins, as well as after carbon monoxide poisoning and in states of cerebral anoxemia (e.g., mountain sickness or sudden fall in blood pressure), are much like histamine cephalalgia. The same holds true for headaches following the use of, or the exposure to, nitrites. Cerebral vasodilatation and distention characterize all these headaches, just as they also explain the headaches in polycythemia vera,

the "postseizure headache and the hypoglycemic or hunger headache

Treatment of this group of headaches should be directed against their respective etiologies, and thus necessitates first of all the diagnosis of the underlying infections

genic substances Horton has introduced the histamine treatment for histamine cephalalgia. The lowered tolerance of individuals suffering from allergic reactions to histamine can obviously not be overcome by a desensitization to histamine since histamine is not an antigenic substance. Yet there is good evidence that histamine given subcutaneously (Horton) or intravenously (Butler and Thomas) may restore the lowered histamine tolerance to normal. The rationale of this treatment can be derived from the generally known fact that individuals suffering from headache under exposure to nitrates will often gradually develop a tolerance to nitrates and lose the headache.

Here again it must be said that the success of the histamine treatment is not specific. We have seen continuous histamine treatment effective in certain patients with different kinds of headaches (as in other vascular disorders) and it is well to remember that many years ago Gowers successfully treated migraine and migraine like headaches with frequent small doses of nitroglycerine.

Horton and his co-workers at the Mayo Clinic have been satisfied with the subcutaneous administration of histamine. They found that 0.1 cc of a histamine diphosphate solution of 1:10,000 was satisfactory as the first dose and they recommend this to be given twice daily increasing it by 0.05 cc until a dose of 0.5 or 1.0 cc of the solution is reached. They continue this last as a maintenance dose and give it one to three times a week. F. K. Hansel found that smaller doses were even more effective and claims success with the sublingual application of 5 drops of a 1:2,000 histamine solution or even of 2 drops of a 1:10,000 solution twice daily.

The usual intravenous histamine treatment consists of the daily administration of 275 mg of histamine diphosphate in 500 cc of isotonic solution of sodium chloride. Most

patients tolerate the infusion of this amount of histamine and fluid given by continuous drip for about 1½ hours or even less. The patient should not develop a headache or a histamine caused fall in blood pressure. Such reactions can be controlled by reducing the rate of flow or by injecting 1 gm of ascorbic acid into the rubber tubing.

Antihistaminic preparations including

patients complain of unpleasant side effects such as drowsiness, sleepiness, dizziness and nausea. Whenever antihistaminic drugs are given the patient should be checked by his physician at least once a week, a blood examination with a differential leukocyte count being made.

The breathing of high concentrations of oxygen should be tried. Wolff and Lennox have shown its constricting effect on pial vessels and Wolff has found it particularly successful in the treatment of headaches associated with carbon monoxide poisoning and other anoxemias, the "postseizure headache" and the so called "hangover headache".

of ergotamine tartrate which is useless in cases of intracranial (pial or cerebral) arterial dilatation and distention. Keeney recommends benzedrine and ephedrine but their efficacy would indicate that the condition under treatment probably belongs in the migraine group (see above).

FREDERICK HILLER

MULTIPLE OR DISSEMINATED SCLEROSIS

Although multiple sclerosis is one of the

logic maladies fill the doctor with a more humiliating sense of helplessness reflects

National Multiple Sclerosis Society may well

supply us with fuller knowledge and with better tools with which to combat this widely incapacitating disease

We know that acute lesions in the central nervous system are characterized by a general sparing of the axis cylinders in the demyelinating process. For this reason many of the clinical manifestations of the acute stage and of acute relapses are reversible. This explains the typical tendency of this malady to spontaneous remissions, which, when they occur following some treatment, only too easily give rise to therapeutic optimism and thus impede discernment of the sound rationale of an apparently successful therapy. Since in chronic cases the pathology consists of foci of sclerosis, e.g., of scar tissue, which of course cannot be influenced by any kind of treatment, whatever therapy may be tried will have to be directed primarily against the clinical manifestations in early cases and against acute aggravations and relapses in later cases.

An objective and critical attitude toward the multiplicity of recommended therapeutic procedures is necessary if we wish neither to deceive ourselves nor to raise false hopes in our patients. It can be safely assumed that every type of therapy used in multiple sclerosis is successful in about 45 per cent of the cases, this percentage of improvement in the patient's condition being approximately equal to that of the occurrence of spontaneous remissions. Nevertheless, most of us make use of one treatment or another because we have the impression that remissions may be aided by our efforts, and that aggravations or relapses of the condition may be prevented. Moreover, we feel that *a hopeful or at least an active attitude on the part of the physician is essential to the patient's morale*.

A brief enumeration of treatments which have been or still are employed appears to be useful. *Gauging over Bruckner's extensive tabulation*, the reader is baffled by the similar ratio of success and failure of the most heterogeneous types of therapy and he is finally convinced that none of the so called specific treatments achieves *much more than* does Nature in the form of spontaneous remissions.

Anti-infectious treatments, including those making use of almost all the heavy

metals, have long been recommended. The belief that multiple sclerosis may be caused by a spirochetal infection has encouraged treatment with neosarsphenamine and silver salvarsin, lately replaced by mapharsen. The intravenous arsenic treatment, the injection of sodium cacodylate in gradually increasing doses, and the administration of Fowler's solution have so often shown a beneficial effect that many physicians, including experienced neurologists, feel that such an effect is not simply accidental. Rather frequently one sees in multiple sclerosis a hypersensitivity to neosarsphenamine, shown particularly by high temperature for a number of days. Although this complicating reaction, necessitating termination of the treatment, has been called undesirable and even contra-indicative, especially good and prompt remissions have been observed after such febrile episodes.

Serum therapy in different forms has been tried in vain. A specific vaccine, such as Purves Stewart thought he had found, has never existed. Nonspecific vaccines have been used as polyvalent vaccines or as antityphoid paratyphoid vaccines in the manner usually employed in artificial fever treatment. Pyrexial methods of this kind, or those involving diathermy (Neymann and Osborne), have been used by all of us with great enthusiasm at first, only to lead once more to doubt and rejection. Malaria treatment was once supposed to help even chronic cases, but almost all cases of more than 5 years' duration did not respond well. Bennett and Lewis met with similar results with the use of diathermy but found that early cases do seem to benefit from this treatment. Most physicians, we think, agree with Freeman, who denies good results from fever therapy, even in acute cases. Besides, fever, at least the kind produced by typhoid vaccines, shortens the coagulation time of the blood, a condition which appears undesirable in view of the circulatory disturbances within the acute foci in the brain. Finally all of us have seen acute exacerbations of multiple sclerosis during a febrile illness!

Roentgen treatment of the spine has been tried in a large number of cases, especially by French physicians, but without convincing results.

Antimyelolytic effects have been attributed to the use of quinine (Brickner). Results of this treatment, too, were disappointing.

Antithrombotic treatment has been introduced, dicoumarin being used as the anti-coagulant. Putnam and his associates have reported on this type of therapy which is neither founded on a generally accepted concept of the pathogenesis of the lesions nor supported by particularly good clinical results. Most vasodilating drugs, such as nicotinic acid, nitrites, papaverine hydrochloride in tolerance doses, as well as aminophylline, have no effect on the clinical course of the disease. That cervico thoracic sympathectomy should be of help, is, a priori most improbable, although a beneficial effect from this, too, has been claimed.

Histamine, H_1 advocated by Horton and used in many cases at the Mayo Clinic, has been tried by a goodly number of neurologists and internists. The 1947 report of the National Multiple Sclerosis Society supports our impression that the daily administration of histamine by intravenous drip (275 mg of histamine diphosphate in 250 cc of isotonic sodium chloride solution) adjusted to the patient's tolerance and given on a full stomach, H_1 generally well received. Although at the beginning, a $1\frac{1}{2}$ hour infusion period seemed optimal, we found that during the course of treatment, this period could be shortened to three quarters of an hour without causing headache and discomfort. Our patients were subjected to from 20 to 30 infusions, but, contrary to the custom in other clinics, we always combined the treatment with complete bed rest. Some of our patients received daily subcutaneous histamine injections (see the chapter on Headaches) for several months after their discharge from the hospital. In the majority of acute cases or in relapses the active hyperemia of the brain brought about by the histamine and the complete bed rest, along with a high vitamin diet and general psychotherapeutic influence, proved successful. To what extent the good results were attributable to the histamine remains an open question which can be answered only on the evidence of wide statistical material. The idea that histamine may serve the purpose of desensitization has been abandoned (see also

the section on the histamine treatment of headaches).

Antiallergic treatment with antihistaminic drugs has yet to prove its value.

General Treatment. Care of patients in the acute or subacute stage of multiple sclerosis deserves much more medical attention than it usually receives. There can be no doubt that the acutely sick patient should stay in bed until all signs of activity of the disease process have disappeared. This holds true not only for recent paresis and paralysis of the extremities, but also for cerebellar, cranial nerve lesions and for signs of retrobulbar neuritis. The bed rest usually brings about both subjective and objective improvement and is recommended as long as such improvement continues. Another indication for bed rest may be a pleocytosis of the spinal fluid, such an increase of cells revealing a meningeal reaction to the underlying lesion of the nervous substance. Such patients should be kept in bed until the cell count has returned to normal. A period of 1 to 2 months may prove necessary. Although there is no proof of a specific effect of vitamins in this illness, they may be given and are certainly indicated in cases with evident vitamin deficiencies and in those complicated by anemia. Concentrated liver extract, 1 cc intramuscularly twice weekly, combined with iron by mouth should be administered. The results of monthly blood transfusions (300 to 500 cc each) have been praised by European neurologists who have seen surprisingly good reactions, particularly in anemic and adynamic cases. Results usually show up within a few days after transfusion and one often sees chronic complaints, such as headaches and paresthesias, disappear. Constipation, a common complaint of these patients must be taken care of by proper diet, and, when necessary, by mild laxatives and enemas. Urinary complications, often an early sign of spinal lesions, may occur in the form of frequency, retention, or incontinence. Treatment corresponds to that followed in myelitis. Great care should be given to urinary infections, which like all infections, tend to have an unfavorable influence on the course of the disease. Urinary antiseptics, diuretics, forced fluids, and, if necessary, tidal drainage will have to be employed. It goes without saying that the

patient should always be examined for any kind of infection and, once located, such foci must be eliminated.

Once the acute phase of the disease has been overcome the patient, even though more or less handicapped, may be able to resume his normal activities, or, if afflicted with severe lasting disabilities, he may be in need of further treatment. In the first instance the physician will be asked how to prevent further relapses, which in our experience threaten all patients with multiple sclerosis. Among known precipitating factors, an important role is played by infections, overexertion and fatigue, chilling, emotional disturbances and pregnancy. Although some women feel even better during pregnancy, onset or relapse of the disease is precipitated in about 40 per cent of female patients. Serious consideration should be given to interruption of pregnancy with sterilization. All patients should be warned against overwork, emotional strain, and exposure to cold and should be told how to protect themselves from infections, especially the common respiratory types which so often lower resistance and precede relapses. Our experience supports Freeman's recommendation as to the value of a southern climate, where multiple sclerosis has been found more rarely than in the north. Those patients fortunate enough to be able to exchange the cold, damp and rapidly changing weather of the northern states for the mild, dry, and stable weather of Arizona, New Mexico, North Texas, and Southern California, should be encouraged to do so, even if only for the winter months.

Symptomatic treatment can often bring improvement to chronic cases, so frequently incapacitated by spastic paresis, ataxia, and cerebellar disturbances. As soon as the acute phase of the disease is terminated, trained physiotherapists should institute re-education by occupational therapy and muscle training, gradually increasing active exercise with the help of warm baths, massage, and mild passive motion of the extremities. It does not further rehabilitation to leave patients to themselves or to order them to remain inactive or even in bed. One should do one's best to avoid the development of spastic contractures and deformities, and, once they have developed, relieve them by

active therapy. Drugs used in combination with physiotherapy include curare and prostigmine. The best results with curare are obtained where spasticity is associated with good voluntary muscle power, but these results are fraught with the danger inherent to the drug D-tubocurarine chloride in oil and wax may be absorbed rapidly or slowly in a rather uncontrollable manner, and dangerous respiratory difficulties may ensue. Furthermore, ataxia may increase or become more incapacitating because of the vertigo following curare. Its use should be restricted to hospitals, or at least to physicians with curare experience. Strangely enough, prostigmine best known as a curare counteractant (see also the section on Myasthenia), benefits at least some cases of spasticity complicated by urinary difficulties, tremor, and weakness. Kabat has used it in cases of from 1½ to 29 years duration with moderate to severe spastic paralysis mostly of a progressive type. Success was attained, notably in cases with less severe paralysis, from daily intramuscular injections of neostigmine methylsulfate (1 to 3 mg with 0.3 mg atropine) usually combined with oral administration of 15 to 30 mg of prostigmine bromide, three times daily for a period of several months to 2 years.

Myanesin (3 ortho toloxy-1, 2 propane diol), the latest of the antispastic drugs has been described by Berger and Schwartz as being ineffective in cases of contracture due to multiple sclerosis. Further studies, however, may change this impression.

Psychotherapy. Psychotherapy in its widest sense is an important factor in the treatment of a disease which affects so many young individuals, strikes with such sudden paralysis or blindness, torments with such incalculability and capriciousness, and fosters such fear of incapacity and helplessness. It is indeed surprising, but is possibly explained by the brain pathology, that not more of these patients show severe reactive depressive disturbances. Relatively frequent are a lack of insight and euphoria which may alleviate mental distress but may also occasionally interfere with the plan of treatment. In multiple sclerosis, hysteria is not only a frequent diagnostic error, but also a complicating factor. Such patients, often bewildered by the coming and going of the

and cures by hypnosis, but more often it explains the good results of reassurance anxiety relief, inspiration with the will to live, and the will to overcome physical handicaps by readjustment. The good physician never tells either patient or relatives that multiple sclerosis is a hopeless, steadily progressive disease. In view of the fact that 5 to 10 per cent of the victims remain able to work with but few symptoms, that about 25 per cent are only moderately handicapped for a period of more than 10 years, and that many are incapacitated only for certain activities, who can make such a statement?

FREDERICK HILLER

REFERENCES

- Bennett A E, and Lewis, N D. Artificial Fever Therapy in Multiple Sclerosis. Study of 51 Cases. *J Nerv & Ment Dis*, 92:202, 1940.
- Bruckner H M. Critique of Therapy in Multiple Sclerosis. *Bull Neurol Inst New York*, 4:665, 1939.
- Ferraro A. Pathology of Demyelinating Diseases as Allergic Reaction of Brain. *Arch Neurol & Psychiat*, 52:443, 1944.
- Ferraro A. Primary Demyelinating Processes of Central Nervous System. Attempt at Unification and Classification. *Arch Neurol & Psychiat*, 37:1100, 1937.
- Freeman W. Frontiers of Multiple Sclerosis. Treatment of Multiple Sclerosis, with Special Reference to Fever Therapy, Prolonged Rest and Climatotherapy. *M Ann District of Columbia*, 13:58, 1944.
- Kabat H. Studies of Neuromuscular Dysfunction, Treatment of Chronic Multiple Sclerosis with Neostigmine and Intensive Muscle Re-education. *Permanent Found M Bull*, 5:1, 1947.
- National Multiple Sclerosis Society. Multiple Sclerosis. Diagnosis and Treatment. *JAMA*, 135:569, 1947.
- Putnam T J, et al. Results of Treatment of Multiple Sclerosis with Dicoumarin. *Arch Neurol & Psychiat*, 57:1, 1947.

PARKINSONISM

Parkinsonism is a descriptive diagnosis synonymous with the manifestations of paralysis agitans, certain postencephalitic states, and disturbances of the extrapyramidal system observed in cerebral arteriosclerosis (known as arteriosclerotic rigidity)

and in various lesions of the brain. The latter are also described as symptomatic parkinsonism and may be the result of severe intoxication, e.g., with carbon monoxide or manganese, but may also result from encephalitides other than epidemic encephalitis. Of the degenerative diseases, hepatolenticular degeneration (Wilson's disease) produces a progressive extrapyramidal syndrome which may resemble postencephalitic parkinsonism.

The treatment of parkinsonism is almost always purely symptomatic, and is directed against the three basic disturbances: hypokinesia, manifesting itself in the reduction or loss of automatic movements, particularly associated synergic movements, and in the paralysis of spontaneity and initiative, muscular hypertonus or rigidity, and tremor.

One, two, or all three signs of the disease may be present, varying in degree from case to case. The three do not react equally well to the same treatment, thus necessitating therapeutic selection according to the preponderance of one or the other of the disturbances. It should be remembered that the characteristic poverty of movement, the anomalies of posture and the loss of facial expression and of mimicry are by no means always the result of muscular rigidity, but may be independent disturbances. Besides the tremor, other hyperkinesias include phasic, tonic, or tetanic muscular contractions, e.g., oculogyric crises, sometimes tic-like involuntary movements, etc. All are resistant to treatment.

The treatment of parkinsonism is a lifetime affair for the patient. This he must understand without discouragement. Many of these individuals accept with relief the fact that their condition is not a true paralysis, and that, if they give their full co-operation, appreciable improvement can be acquired and maintained. Fortunately, many cases, especially those of postencephalitic parkinsonism, become stationary after a number of years, and thus permit these patients, if properly treated, to continue useful lives and to get along much better than they would without any treatment at all. We shall

tient should be told about the dryness of mouth and the difficulties of accommodation that he will experience but which are usually overcome with time. Most patients compensate for the lack of saliva by chewing gum or by sucking fruit drops. Others just accept the fact. If necessary, pilocarpine nitrate, 5 mg or more, several times daily will alleviate the mouth dryness as well as the disorders of accommodation.

In a great number of patients hyoscyne (scopolamine hydrobromide) has proved to be not only an efficacious but a reliable drug over long periods of time. Patients easily adjust themselves to the required dosage, habit formation appears to be almost negligible, and unpleasant side effects are controllable. In cases of average severity the minimum dose is 0.5 mg three times daily, given by mouth in tablet form. In milder cases or in apprehensive patients 0.25 mg can be tried, the dose being gradually increased to 1.5 to 2 mg daily. A severe rigidity often demands much larger doses, and many of these patients finally take a regular daily dose of 10 mg without ill effects, although such a dose would have an extremely toxic effect on a normal individual. Quite similar is the effect of atropine sulfate in the same dosage. Resistant cases have been treated successfully for months with doses as high as 20 mg three times daily. The danger of cardiac complications and of toxic psychotic reactions must be kept in mind, and the patients should be closely watched. Stramonium appears to be most useful in combination with scopolamine when this drug cannot be taken in sufficient amounts. It may be given as tincture in doses of 25 drops up to 1 teaspoonful three times daily, or in powder form (in pills or capsules), 0.5 to 2.0 gm as the total daily dose. Bulgarian belladonna, originally a white wine decoction of Bulgarian belladonna root, can be obtained in tablet form as bellabulgara. Fabing and Zelig found the wine extract from the USP belladonna root just as effective. Patients who do not respond favorably to the other drugs named above may be given bellabulgara, which is supposed to be more effective in smaller doses. A like claim is made for compounds of belladonna alkaloids, such as rabellon. In every case the individual optimal dosage must be established.

Since Price and Merritt's report on the treatment with wine extracts of Bulgarian belladonna, synthetic products with all the good effects of the belladonna group of drugs but with less toxic manifestations have been tried. Berger and Schwartz have found that the oral administration of myanesin (about 1 gm daily) is useful in reducing not only the rigidity but also the tremor. Hartmann has reported on a product called parpanit, which seems to have a good effect on the rigidity. The reader will find more detailed information of this and of all these products, the value of which is yet to be proved, in the recent publications of Schwab and Leigh.

Contraindications to treatment with the belladonna group include certain psychic disorders which may complicate postencephalitic parkinsonism. States of mental and emotional excitement and hallucinatory and paranoid conditions are aggravated by too large doses of belladonna and related drugs. There is hardly any doubt that large doses of these alkaloids may of themselves produce toxic manifestations, such as dizziness, forgetfulness, confusion, lethargy, and hallucinations, and lead to mania and prostration. Organic debility of various types also may require caution in the dosage of these drugs.

Curare, as d-tubocurine, has no place in the treatment of the average type of parkinsonism, but it may be considered in those helpless and hopeless final stages of total rigidity where nursing care and nutrition have become almost unsurmountable problems.

Amphetamine (see page 653) is added. This is probably explained more by its effect on the extrapyramidal mechanisms, although the stimulation of effective reactions (i.e., subcortical functions) obviously plays an important role. The dosage varies from case to case. Usually 5 mg of benzedrine or dexedrine sulfate given in tablet form with the first two doses of scopolamine (at breakfast and lunch) are well supported and may be doubled if necessary. Amphetamine

serves to be tried

The hyperkinesias, especially the tremor, are unfortunately rather refractory to all these therapeutic procedures. Other drugs

a limited time (The reader is referred to the section on Epilepsy) Hemilateral severe tremor, which may reach such a degree as to become a torture to the patient, can be relieved by surgery. Bucy has described the abolition of tremor by extirpation of a small portion of the cortical motor area (47). The freedom from tremor will have to be paid for by some motor weakness.*

Almost every case of parkinsonism benefits from exercise, gymnastics, massage, and other physiotherapeutic procedures. The physician who continuously and energetically insists on this part of the treatment will rarely be disappointed. Any sports, such as bicycling, rowing, bowling, swimming, etc., may be employed to the same good end. Many of the excellent results obtained with Bulgarian belladonna in Europe were due to the emphasis placed on gymnastics. Physical exercise has proved helpful not only mechanically but also psychotherapeutically. This has been part of the secret of success of those treatment centers for postencephalitic parkinsonism sponsored by the former Queen of Italy, where daily group exercises accompanied by stimulating music, formed part of

* Doshay and Constable have recently advocated the use of trihexyphenidyl marketed under the trade name of artane, as a valuable drug in the treatment of parkinsonism. This preparation may be used independently or in conjunction with other drugs.

administer the drug before meals to diminish salivary flow. The toxic effects of artane are minimal.

Editor
Doshay, L. J., and Constable, Kate. Artane Therapy for Parkinsonism, *JAMA*, 140 1317, 1949

the therapy. We should remember that strong emotional reactions, precipitated not only by panicky fright but also by joyous elation can break through as severe hypokinesia and a considerable amount of hypertonicity. The pleasurable character of the treatment and the ambition it arouses in the patient to win over his slowed down feeling can contribute decisively to therapeutic success.

FREDERICK HILLER

REFERENCES

- Berger F M, and Schwartz, R P. Oral "Myanesin" in Treatment of Spastic and Hyperkinetic Disorders. *JAMA*, 137 772, 1948.
Bucy P C. Surgical Relief of Tremor at Rest. *Ann Surg*, 123 933, 1945.
Fabing H D and Zelig, M A. Treatment of Postencephalitic Parkinsonian Syndrome, with Desiccated White Wine Extract of *USP* Belladonna Root. *JAMA*, 117 332, 1941.
Hartmann K. The Use of Parpanit in Neurological Cases. *Therap Rev*, 3 163, 1947.
Price J C and Merritt H H. Treatment of Parkinsonism. Results Obtained with Wine of Bulgarian Belladonna and Alkaloids of *USP* Belladonna. *JAMA*, 117 335, 1941.
Schwab R S, and Leigh D. Parpanit in Treatment of Parkinson's Disease. *JAMA*, 139 629, 1949.

EPILEPSY AND THE CONVULSIVE STATE

The title of this section is selected because treatment in any instance must be directed toward orienting the patient and his family who are sensitive to the word "epilepsy" with its social implication. We have come far from the dictum of John of Gaddesden, mentioned in Chaucer's *Canterbury Tales*, 1344, who said an epileptic "should not mingle with people to any extent, on account of the presence of his betters—before whom he is ashamed and by thinking of his condition, he falls." "Epilepsy" is derived from a Greek word meaning "seizure." This seizure is caused by some disturbance in the body. The convulsion or fit is only a symptom, just as "cough" in pneumonia, or "dyspnea" in heart disease. The whole concept of stigma, social isolation, economic and educational handicap must immediately be corrected and the patient and family occupied with the problem of determining the origin of the epileptic state.

This means a complete medical, neuro-

mental torpor, and are useful even when the newer drugs have failed

BARBITURATES These are essentially (1) phenobarbital (5, 5 phenylethylbarbituric acid) introduced for clinical trial in 1912 as a sedative and a hypnotic and tried in epilepsy by Hauptmann and (2) mebaral (3 methyl 5, 5 phenylethylbarbituric acid), reported by Heyde and Blum in 1932 as a useful antiepileptic drug

Phenobarbital is an effective substance against grand mal, jacksonian and convulsive attacks with localizing symptoms. It is cheap but a bit more expensive when bought under trade names such as luminal and gardenal. The principal limitation is its sedative effect but individual susceptibility varies. Early, most patients feel drowsy but this disappears. The drug is excreted slowly so that it may be taken only once or twice daily. When well tolerated phenobarbital may be used for years without ill effect and without habituation. Some patients, taking one 0.1 gm tablet at night, have been fit free for as long as 15 years.

However, one danger exists. If the drug has been used for years, abrupt withdrawal may be followed by an exacerbation of symptoms or even a status epilepticus. When taken in huge amounts by mistake or with suicidal intent, the individual develops ataxia, coma, respiratory depression and may even die. Picrotoxin and metrazol are antidotes, with oxygen and similar supportive measures. A susceptible patient may develop a scarlatiform rash.

Phenobarbital is dispensed in tablets of 0.015, 0.03, and 0.10 gm, as an elixir containing 0.015 gm per teaspoonful or as a soluble sodium salt which can be used parenterally. The drug may be combined with bromides, hydantoin, tridione, phenurone, etc. With some combination as occasionally in a phenobarbital-mesantoin mixture excessive drowsiness may occur.

Mebaral or prommal, the N-methyl derivative of phenobarbital, is a barbiturate homologue of mesantoin. The antiepileptic properties are less than those of phenobarbital. Some like to use it for petit mal attacks, others like it as a supplement to tridione and also to reduce the possibility of a grand mal attack.

The dosage is double that of phenobarbital,

and the drug is dispensed in 0.03 and 0.2 gm tablets. Somnolence, as with phenobarbital, may limit the total daily dosage which may vary from 0.10 to 0.6 gm.

HYDANTOINS These are essentially two, sodium diphenylhydantoin (dilantin sodium) and mesantoin.

DILANTIN SODIUM, epanutin, or phenytoin sodium, (5, 5 diphenylhydantoin) was recommended for clinical trial in 1937 by Putnam and Merritt as the result of a formal laboratory experiment to find antiepileptic drugs. Within a year the effective anticonvulsant effects were confirmed. The use of dilantin sodium was recommended in psychomotor epilepsy in related behavior disorders and in symptomatic epilepsy. Here for the first time was an antiepileptic drug which was not hypnotic. Unpleasant side effects are several and are often seen at the effective therapeutic level. Two or 3 per cent develop a morbilliform rash. A rare patient may develop a hemorrhagic reaction which on two occasions has been part of a fatal outcome from intake of the drug. Muscle incoordination with ataxia of gait, tremor, nystagmus, diplopia,

plasia may occur, but this is usually amenable to dental care or to simple oral hygiene and vigorous massage. Hirsutism appears rarely in adults. A few patients may suffer from weight loss, drowsiness, fatigue, and even a psychotic episode.

Generally the drug is administered in effective easily controlled dosages or combined with other drugs, phenobarbital, bromides,

from 0.30 to 0.60 gm per day and children proportionately less.

After prolonged intake of dilantin sodium a previously fit free patient may have a seizure. Then combination with other drugs may be necessary.

MESANTOIN, 3-methyl-5, 5-phenylethylhydantoin, was reported in 1945 and 1946 by Loscalzo, Klein, Kozol, Lennox and Marburg and Helfand who showed that this drug could control many patients with grand mal or psychomotor epilepsy who were refractory to dilantin sodium or other medication.

Others have stated that mesantoin is of no benefit to petit mal epilepsy

The toxicity is somewhat greater than that of dilantin sodium in that a substantial number of patients develop a generalized rash swollen lymph nodes in the scalp and neck and fever Drowsiness and fatigue may also limit the dosage Mesantoin has good anti convulsant qualities and produces neither ataxia nor gingival hyperplasia As indicated above it may be combined with other drugs used in the treatment of epilepsy The tablet comes in one size 0.10 gm but a crease through the center enables easy division into 0.05 gm dosages The usual adult daily dose is 0.80 gm but as many as 9 tablets per day may be taken The combination with phenobarbital produces an effective antiepileptic substance but profound drowsiness may ensue

THE DIONES These are two tridione and paradione

Tridione or 3,3,5 trimethyl-5-oxazolidine-2,4-dione was synthesized and first reported to have analgesic properties by Spielman Everett and Richards in 1944 showed that tridione raised the threshold for chemically and electrically induced convulsions There is as yet no laboratory test for distinguishing drugs which would be effective against petit mal The specificity of tridione in the treatment of petit mal attacks was reported briefly by Perlstein in 1945 Lennox and others have confirmed these results and our experiences have been in consonance

Tridione is a remarkable drug against petit mal It may even have value in some psychomotor seizures when combined with dilantin sodium or phenobarbital It is generally conceded that tridione is somewhat of a convulsant per se and may increase the frequency of convulsions When grand mal

wear dark glasses The sensitivity wears off after the drug has been discontinued

A more serious complication is a depression of the bone marrow activity First a leukopenia occurs with a depression of the granulocytes Later the other blood elements become implicated so that an aplastic anemia ensues Several fatalities have been reported It becomes necessary therefore to follow all cases with frequent blood counts If the neutrophil count drops below 1600 per cubic millimeter the drug must be discontinued A relatively infrequent side effect is lethargy Nephrosis is also a rare complication

Tridione is dispensed in capsules contain

per day depending on the age of the patient and the need of the case

Paradione 3,5 dimethyl-5-ethyl-oxazolidine-2,4-dione was developed by Everett and Richards in the continuation of the research on oxazolidine diones It differs from tridione in the substitution of an ethyl for a methyl

patients who did not respond to the former

The over all effects of the two drugs are similar Paradione produces less photophobia is less toxic to the bone marrow and is less convulsant but it is also less effective in stopping petit mal attacks

Paradione is supplied in 0.3 gm capsules of which 2 to 5 may be required daily Blood counts and observations of mucous membranes are carried out as with tridione When grand mal attacks coexist dilantin sodium phenobarbital mebaral or mesantoin is appended to the regimen

PHENURONE Phenurone phenacetylurea has recently been added to the antiepileptic drugs through the studies of Gibbs Everett and Richards It has been reported as useful in grand mal petit mal and particularly in psychomotor seizures The greatest danger in use of this drug is with regard to the last group Phenurone tends to bring out and exacerbate previous personality deviations Therefore one must be on the lookout for released impulsive behavior psychosis and suicidal attempts All have been reported in

severe and occasionally dangerous side effects There is the usual rash of morbilliform character which clears with cessation of therapy and which may not be too severe if the drug is reinstituted slowly A strange side effect is photophobia on exposure to sunlight hemeralopia There is no known permanent damage to vision and the patient need only

patients taking phenurone Individuals on this drug require the closest watching to rule out sensitivity

Other unpleasant side effects are anorexia which can be combated with large dosages of vitamin B complex tingling of the hands and feet palpitation and insomnia A rare rash and hepatitis have been reported and one of our patients invariably developed fever and leukopenia (no neutropenia) while on phenurone All of these disappear when the drug is discontinued

On the positive side however phenurone

with any of the other antiepileptic substances to produce more desirable over all effects

Adjuvant therapy in the treatment of epilepsy includes glutamic acid amphetamine and dexedrine caffeine ketogenic diet and dehydration

dullness I have never seen any of these salutary effects

AMPHETAMINE DEXEDRINE and CAFFEINE are of aid in combating the drowsiness of some of the antiepileptic substances and may be of use in the petit mal group where the spell is associated with a slow brain rhythm Caffeine is administered in dosages of 0.1 to 0.3 gm daily amphetamine up to 0.030 gm and dexedrine to 0.015 gm daily

KETOGENIC DIET is often beneficial in petit mal and myoclonic epilepsy However the

DEHYDRATION REGIMENS introduced by Fay came along with the studies on pitressin hydration tests for producing seizures The method is impractical over a long period necessary to control a given case of epilepsy

Status Epilepticus This is the great emergency of epilepsy and requires immediate treatment The repeated seizures must be

require repetition If such drugs are not available ether by mask may be tried Avertin per

rectum is a useful drug and some advocate 10 cc of a 25 per cent solution of magnesium sulfate

Meanwhile the patient should be in a bed with padded side rails and adequate parenteral fluids (the patient usually in coma or vomiting) with glucose and salt given to maintain fluid balance and keep the fever down Hypertonic glucose may be of value A maintenance dosage of sodium phenobarbital intramuscularly and sodium bromide by rectum is started Constant attendance is essential to prevent the patient from biting his tongue and injuring his limbs

As soon as the person can swallow the usual regimen of antiepileptic drugs is started but the parenteral route is used until the enteral intake is established

Furor States and Excitements These require special care because of danger to the patient and those about him While sedation and packs may control some many such episodes can be terminated only by giving the patient one or more artificial seizures Weinberg used metrazol but we have achieved excellent terminations of these states by use of electroshock treatment

Autonomic Diencephalic Fits These should respond to sympathetomimetic and parasympathetomimetic drugs but I have obtained one good remission in such a syndrome by progressive histamine desensitization

In conclusion therefore there is no single drug which suits any one type of patient Drugs dosages and combinations must be varied even in the same person who had been fit free previously for a long time until the desired remission is obtained Above all the

enough achieved but each year brings the answer closer to these many people who need help

BENJAMIN BOSCHES

REFERENCES

Blum E Die Bekämpfung epileptischer Anfälle

- Clein N W New Anticonvulsant in Treatment of Epilepsy 3 methyl 5 5 phenylethylhydantoin (Hydantal) Preliminary Report Northwest Med 41 210 1945
- Davis J P and Lennox W G The Effect of Trimethyloxazolidine Dione and of Dimethylethyl oxazolidine Dione on Seizures and on the Blood in Epilepsy *Proc A Research & Ment Dis* 26 423 1947
- Everett G M and Richards R K Personal communication
- Everett G M and Richards R K Comparative Anticonvulsive Action of 3 5 5 trimethyloxazolidine 4-dione (Tridione) Dilantin and Pheno barbital *J Pharmacol & Exper Therap* 81 402 1944
- Fay T Therapeutic Effect of Dehydration on Epileptic Patients *Arch Neurol & Psychiat* 23 920 1930
- Freyhan F A Effectiveness of Diphenylhydantoin in Management of Nonepileptic Psychomotor Excitement States *Arch Neurol & Psychiat* 53 370 1945
- Gibbs F A Epilepsy Social Aspects Electroencephalographic Classification and Treatment Lecture of Resident Staff Veterans Administration Hospital Hines Illinois 1948
- Gibbs F A New Drugs of Value in Treatment of Epilepsy *Ann Int Med* 27 548 1947
- Gibbs F A Everett F A and Richards R K Presented before American British International League Against Epilepsy June 13 and 14 1943 Atlantic City N J
- Hauptmann A Luminal bei Epilepsie *Muenchen med Wchnschr* 54 1907 1912
- Heyde W Ueber Prominal und Luminal Wirkung bei schweren epileptischen Erkrankungen *Klin Wchnschr* 11 1874 1932
- Jasper H and Kershman J Electroencephalographic Classification of Epilepsies *Arch Neurol & Psychiat* 45 903 1941
- Keth H M Results of Treatment of Recurring Convulsions (Epilepsy) *Proc Staff Meet Mayo Clin* 29 14 1947
- Kozol H L Epilepsy Treatment with New Drug 3 methyl 5 5 phenylethylhydantoin (Phenatoin) *Am J Psychiat* 103 154 1946
- Lennox W G and Lennox W G *JAMA* 134 138 1947
- Lennox W G Newer Agents in Treatment of Epilepsy *J Pediat* 29 859 1946
- Lennox W G Petit Mal Epilepsies Their Treatment with Tridione *JAMA* 129 1069 1945
- Lennox W G Treatment of Epilepsy *M Clin North America* 29 1114 1945
- Marburg O and Helfand M Analysis of 100 Cases of Epilepsy *J Nerv & Ment Dis* 104 465 1946
- Merritt H H and Putnam T J Sodium Diphenyl Hydantoin in Treatment of Convulsive Seizures Toxic Symptoms and Their Prevention *Arch Neurol & Psychiat* 47 1053 1939
- Merritt H H and Putnam T J New Series of Anticonvulsant Drugs Tested by Experiments on Animals *Arch Neurol & Psychiat* 39 1003 1938
- Moore M T Symptomatic Abdominal Epilepsy *Am J Surg* 72 583 1948
- Paskind H A Extramural Patients with Epilepsy with Special Reference to Frequent Absence of Detention *Arch Neurol & Psychiat* 23 370 1939
- Perlstein M A and Andelman M H Tridione Its Use in Convulsive and Related Disorders *J Pediat* 29 20 1946
- Price J C Waelisch H and Putnam T J DL Glutamic Acid Hydrochloride in Treatment of Petit Mal and Psychomotor Seizures *JAMA* 122 1153 1943
- Putnam T J and Merritt H H Dullness as Epileptic Equivalent *Arch Neurol & Psychiat* 45 797 1941
- Putnam T J and Merritt H H Experimental Determination of Anticonvulsant Properties of Some Phenyl Derivatives *Science* 85 525 1937
- Richards R K and Perlstein M A Tridione A New Experimental Drug for Treatment of Convulsive and Related Disorders Clinical Investigations *Arch Neurol & Psychiat* 55 164 1946
- Spielman M A Some Analgesic Agents Derived from Oxazolidine 2 4-dione *J Am Chem Soc* 66 1244 1944
- Wernberg J Control of Epileptic Furors and Epileptic Excitements Annual Meeting, Cincinnati O May 20 to 24 1940 American Psychiatric Association

NARCOLEPSY

The treatment of narcolepsy depends a great deal on the diagnosis and while this particular book does not deal with diagnosis per se it is essential that certain points be emphasized

Narcolepsy or the tendency toward sleepiness is a symptom of many diseases which may vary from encephalitis brain tumor chronic uremia or heat exhaustion to altered metabolic states such as hypothyroidism or the complications of diabetes ketosis Many individuals under stress and strain become withdrawn and "sleepy" even the catatonic withdrawal of the more major psychiatric reactions is interpreted as sleepiness

In this section however narcolepsy will be limited to Gelineau's syndrome characterized by sudden attacks of

ing sleep and by associated bouts of cataplexy on emotional stimulation. The individual loses muscle tone so that he may drop. Acute excitement, laughter, anger, or surprise can leave the person absolutely help-

quently amenable to the action of the amphetamines. Among these drugs may be mentioned amphetamine sulfate (proprietary benzedrine sulfate), racemic amphetamine sulfate, 1 phenyl 2 amino propane sulfate, d amphetamine sulfate, the other names (proprietary dexedrine sulfate) d 1 phenyl 2 amino propane sulfate, d benzedrine sulfate, methamphetamine hydrochloride, other names (proprietary desoxyn norodm hydrochloride) d desoxyephedrine hydrochloride, the hydrochloride of the diisomer of n methyl betaphenyl-isopropylamine (1 phenyl 2 methylamino propane) Ephedrine sulfate, otherwise 1 phenyl 2 methylamine-propanol 1-sulfate, is also of use in narcolepsy.

Amphetamine or benzedrine sulfate is a potent sympathetcomimetic and central nervous system stimulant, counteracting sleepiness. It comes in 10 mg tablets and is given in 20 to 40 mg dosage, once or several times during the day, as required. Late dosages are avoided to prevent interference with regular sleep. It is contraindicated in severe cardiovascular disease, marked hypertension, or hyperthyroidism. Danger of habituation exists.

produce the irritability, the peripheral vasoconstriction and the elevation of blood pressure of ordinary amphetamine sulfate. In narcolepsy it is given in 10 to 25 mg doses at intervals through the day.

D desoxyephedrine hydrochloride, or desoxyn counteracts sleepiness without marked peripheral pressor effects. It comes in 25 mg tablets.

The action of the three amphetamines is essentially similar, the equivalents being 10 mg amphetamine sulfate (benzedrine sulfate), 5 mg d amphetamine sulfate (dexedrine sulfate), and 25 mg of desoxyn. Benzedrine sulfate is probably the most effec-

tive antinarcotic but it has the greatest number of side effects. Among these may be mentioned anorexia, loss of weight, jitteriness from the stimulating effect, and occasionally elevated blood pressure. It may be necessary in some cases to increase the dosage of these drugs or to spread the administration over several dosages during the day.

Another drug sometimes of value is ephedrine sulfate in dosages of $\frac{1}{2}$ gram (25 mg) two or three times per day, as needed.

It is again emphasized that the type of narcolepsy described here is that limited to the sleepiness with cataplexy. The type asso-

ciated with a tumor of the third ventricle, encephalitis, or metabolic disturbances are treated according to their causes. Even in these disorders, the amphetamines and ephedrine sulfate may give symptomatic relief.

BENJAMIN BOSKES

THE PARAPLEGIC STATE IN LESIONS OF THE SPINAL CORD

Physicians in general practice frequently encounter a paresis or paralysis of the legs, usually including also that of the bladder and rectum. Occasionally, when the lesion reaches into the cervical spinal cord the upper extremities may be involved, as may the cranial nerves and parts of the brain when the disease is not limited to the spinal cord. Treatment of a paraplegia is, of course, dependent first of all on a correct understanding of the cause of this paralysis. In this respect each case will differ. One may have to deal with an extramedullary lesion whereby a compression syndrome results from a tumor, from an epidural abscess pressing on the spinal cord, from a vertebral dislocation, or from the destruction of one or more verte-

brales. In other cases the lesion is intramedullary, due to an or the continuity of the cord. In other cases the lesion will be diagnosed as intramedullary, and may be caused by a myelitis, infectious or toxic in origin, by a tumor, by a traumatic lesion destructive, contusional or hemorrhagic, or by a primary circulatory, i.e., ischemic, lesion. Specific treatment will de-

Then and there will it be decided whether

the paraplegic state will be discussed here with the understanding that it may have to be preceded or accompanied by a specific treatment which will vary in every case

A few words only may be said as to the handling of acute traumatic paraplegics. These patients should not be moved until the necessary means of transportation and sufficient help are available. The head should not even be raised. Three persons are required to slide the patient gently on the litter or to any firm surface used for transportation. One man should use a steady traction on the head, another on the feet, and the third should take hold of the patient's clothing and thus pull him over on the litter. The site of the spinal fracture or dislocation should be kept in slight hyperextension, which is best achieved by putting a folded blanket under the shoulder blades or under the lumbar spine. As a rule, it is much safer to transport the patient in the supine position, although certain spinal fractures may do as well, or occasionally somewhat better in the prone position. Administration of morphine may be dangerous, particularly in high cervical cord lesions. The acute root pain is often alleviated by the traction and by the body

interruption of the cord exists. The attending physician must often avail himself of the

therapy

Spinal surgery indications must be determined as early as possible. This holds true in all those paraplegias where a compression syndrome has resulted from any condition which strangulates the spinal cord. An extramedullary abscess or tumor, a vertebral dislocation or fracture, or a disease process in one or several vertebrae—all may cause what is generally understood by the term, spinal block. A spinal puncture with performance of Queckenstedt's test will determine the presence or absence of a complete block, but in a case of severe compression of the spinal cord an incomplete block with a considerable narrowing of the lumen of the subarachnoid space may still show an almost normal rise of spinal fluid pressure on jugular compression. In nontraumatic cases a possible block should be verified as soon as possible, and the laminectomy decision left to a neurosurgeon or surgeon. In spinal injuries the decision to subject the patient to surgery is far more complicated. Such injuries with vertebral fractures or dislocations, demand, first of all, immobilization of the patient. Since lumbar puncture may be harmful to him, we therefore agree with John Martin's statement "only those patients should have lumbar puncture manometric tests who can be helped by operation." He considers "laminectomy indicated in compression injuries of the cord only if there was an incomplete lesion and the patient was showing progressive loss of function, and the loss of function could not be arrested by close manipulation." Laminectomy in cervical injuries during the first few days, even in the presence of a block "is certain to be the one instance in which surgery contributes to the already poor prognosis of the patient." Since in many cases, the anatomic and physiologic interruption of the continuity of the spinal cord cannot be differentiated, most surgeons agree that the presence of a block in the thoracic region, particularly with roentgen-ray evidence of severe bone injury, indicates laminectomy, even in the presence of a complete functional loss below the lesion. In

chance to live through the usually many months of slow restitution or adaptation without suffering serious harm or even succumbing to the complications which threaten him in his paralyzed condition. On the care and handling of these patients depends the final outcome of a paraplegia regardless of whether the anatomic continuity of the spinal cord is interrupted or whether only a more or less complete physiologic or functional in

juries to the cauda equina offer far fewer contraindications to surgery and should be explored if there is roentgen ray or clinical evidence of root fiber compression or impingement by bone fragments

After the patient has overcome his primary shock spinal injuries with or without injury to the cord should possibly be corrected. In injuries to the thoracic or lumbar spine the various methods of keeping the patient in hyperextension are indicated. Injuries to the cervical spine are best treated with the application of head traction by means of the Crutchfield tongs. The often severe root pains are usually relieved by traction and immobilization.

Nursing care problems in relation to paraplegics center about lost or severely impaired sensation and motion visceral and sympathetic disturbances below the level of the lesion and frequent motor phenomena originating in a spinal cord more or less completely severed from the controlling and integrating function of the brain. Most of these cases are chronic and the morale of the patients depends greatly on the type of general treatment and on the psychologic attitude of the nurses and physicians.

Dccubitus ulcers have such a detrimental effect on the well being of these patients and render their care so much more difficult that they must be prevented at all costs. Nothing leads so easily to the development of ulcers as constant pressure on anesthetic tissues particularly when associated with maceration of the epidermis by moisture such as sweat urine feculent material etc. Plaster casts therefore should be avoided or at least most carefully applied and watched. The turning of the patient at regular intervals (every 1 or 2 hours) prevents damaging pressure upon weight bearing points. The

Stryker frame permits turning the immobilized patient 180° allowing him to lie alternately on his back or on his abdomen. Skin hygiene (washing massage alcohol rubs zinc powder or talcum etc.) is as essential as the careful smoothing out of the bed sheet and the prevention of soiling by urine and feces. The use of urinals or absorbent material over the perineum the regulation of defecation the use of a firm mattress (if necessary a so called split mattress) have proved of great value. The danger of exces-

sive heat applications over anesthetic areas should be explained to the nurses. The frequent profuse sweating can be mitigated by occasional injection of 0.4 mg. of atropine. Once ulcers or bedsores have developed dressings with sulfa powder or penicillin the use of ointments or the painting of the sore skin with tincture of benzoin are preferable to moisture incision drainage or débridement. The healing process is facilitated by the use of sponge rubber air or water mattresses and by ultraviolet light. Large and deep ulcers require surgery preceded and followed by penicillin therapy. The ulcer must be excised in its totality and the underlying bony prominences should also be removed. Tissue flaps turned or grafted on such a clean and well vascularized wound usually heal under a moderate pressure dressing.

Nutrition should be sufficient (about 2500 to 3000 calories daily) and should be rich in protein and carbohydrates. Vitamins in the form of multiple vitamin capsules are to be

Amigen or amino acids may be added to the diet. Fluid intake should be generous. The frequent achlorhydria in chronic paraplegics may be compensated by diluted HCl with meals. Anemia which occasionally develops may benefit from liver and iron administration.

Care of bladder and rectum is of greatest importance. Not only is the urinary paralysis the most frequent and dangerous source of ascending infections (urinary sepsis has been the outstanding cause of insufficient and failing spinal reflex activity and finally of death and is still one of the gravest problems in chronic cases) but the lack of urinary and rectal control makes a paraplegic or paraparetic more of a cripple less fit to integrate himself again into human society.

Any severe spinal cord lesion may show bladder paralysis in the beginning. In incomplete lesions only time can tell whether the patient will regain his full or partially normal function of micturition or whether his bladder will retain one or another form of insufficiency. Where the patient has lost voluntary control over his bladder treatment aims at the establishment of an "automatic

micturition. Such treatment will also be helpful in furthering the restoration of partial voluntary bladder control. Should this state develop in time. An automatic bladder may develop following lesions at any level of the spinal cord but develops more promptly in those above the middle of the thoracic cord. Lower cord and especially cauda equina lesions are more often associated with a tendency to urinary retention increase of bladder capacity and incontinence. Yet after many months of good care overcoming of infection and co operation of the patient an automatic bladder may be achieved even in lower cord injuries.

A paralyzed bladder will first develop retention of urine followed by overflow and incontinence. If not properly managed such a bladder may rupture and it is generally agreed that distention and overflow are harmful. The arbitrary intermittent use of a catheter is bad since it facilitates urinary infection and sepsis and prevents the establishment of an automatic bladder. Manual expression of the full bladder may lead to rupture and often aggravates an existing infection. The best initial treatment of the paralyzed bladder is probably the so called tidal drainage a rather complicated procedure which can be carried out only in a hospital by those experienced in this method.

For this reason these patients are usually treated by introducing into the bladder a number 18 Foley catheter which is small enough to permit the escape of urethral secretions into the bladder or externally. An indwelling catheter such as this should be opened for drainage every 4 hours and should be closed with a stopcock. Three times during the day and once at night irrigations with some urinary antiseptic are necessary. Regular cystometric control gives information on the degree of muscular tone of the bladder and indicates when the catheter may be removed and the automatic emptying of the bladder be expected. The efficiency of an automatic bladder depends on the patient's ability to achieve micturition at a desirable moment e.g. when the bladder contains about 300 to 500 cc of urine. When the lesion is above the lower third of the thoracic cord this state of bladder distention is usually felt as sudden heat flushing and perspiration over the upper half of the body. The patient

then learns to initiate urination by the use of external stimuli e.g. rubbing the skin of the abdomen or that of the inguinal region tugging on one spermatic cord or pinching the skin of the thigh. A good automatic bladder should empty itself when it contains 400 to 500 cc of urine and should retain less than 100 cc. Such patients will empty the bladder about four times daily and may pass the night without voiding depending on the amount of fluid intake. General muscular spasticity tends to diminish the bladder capacity and is often accompanied by frequent uncontrollable emptying of small amounts of urine.

Lower thoracic lumbar and caudal lesions usually do not produce the viscerovisceral reflexes and the initiation of an automatic emptying of the bladder often depends on a sensation of fullness in the abdomen. Some times automatic micturition follows transurethral resection of the bladder neck. This operation may be of value to patients with an automatic bladder impaired by retention due to spastic sphincteric contraction.

The decalcification of the bones in recumbent paraplegics the excretion of large amounts of calcium through the kidneys together with some bladder infection often lead to stone formation in the bladder a condition which should be checked by bi-monthly x rays. A fluid intake of over 3000 cc combined with urinary antiseptics helps to reduce this complication. Bladder stones will have to be removed. Stone formation in the kidney pelvis and the passing of a stone through the ureter may betray themselves only by a rise in temperature.

General experience has shown that patients with chronic cases of paraplegia kept alive with the help of modern antibiotic drugs can and must learn to empty the bladder automatically but it has also been observed that automatic micturition is easily lost if the patient does not get proper care or if he fails to co operate. Relatively rare patients with completely flaccid sphincters may have to wear a urinary constantly.

The often disturbing priapism which may be seen in compression or transverse syndromes alike responds to camphor mono-

Care of the paralyzed rectum aims at automatic defecation. After a short period of complete depression of automatic function during the state of spinal shock the rectum will respond to stretching which causes contraction followed by relaxation. Even though automatic defecation will develop in the presence of a spastic or flaccid sphincter, it has been found that lower spinal cord and caudal lesions are those most frequently followed by a satisfactory automatic defecation. At first, the patient lying on his abdomen should receive enemas every 3 days only, and the formation of scybala may be avoided by the use of cathartics such as mineral oil, cascara, metamucil, etc., for a few days in the transition period. The sooner after a cord lesion reflex defecation is taught, the better. First the attending nurses, then the patient himself, should stretch the rectal sphincter with the lubricated gloved finger. Soon reflex rectal contraction and defecation will occur after slight stimulation of the skin near the anus, and eventually the patient will be able to defecate sitting on the toilet, compressing his diaphragm and using manual pressure on his abdomen.

Treatment of pain becomes a necessity, not only in traumatic cord lesions but also in extramedullary tumors and in those cases where tumor metastases have invaded the spinal column. Traction and immobilization often stop the root pain in vertebral dislocations and fractures. Injuries impinging on

posterior root fibers, can be relieved by posterior rhizotomy. In the presence of lasting and severe pain below a cord lesion, not indicative of a root pain, cordotomy may be indicated, but not for pain in caudal lesions.

Particular attention is to be given to the use (and eventually abuse) of narcotics. That drug addiction is a dangerous complication in spinal cord lesions is testified to by the many patients so addicted who suffer pain or painful distress which defies treatment. Psychotherapy should be given a chance in these cases.

Treatment of muscle spasm in spinal cord lesions, both complete and incomplete, is a problem which has not been solved. These

spontaneous or induced flexor or extensor spasms are more frequent and distressing the higher the lesion. Since spontaneous improvement may occur, radical operations, such as extensive anterior or posterior rhizotomy, should be reserved for chronic cases with complete physiologic transverse lesions of the cord. Such patients who are in danger of developing unmanageable decubitus ulcers and show an increasingly hypertonic bladder, often become much easier to care for after section of the anterior roots, D_2 to S_1 . In such cases a subarachnoid injection of 10 to 15 cc of absolute alcohol between L_1 and L_2 may be considered. As a method, alcohol injection is of course, much simpler than the rhizotomy and quite as effective if done in the proper way, with the patient's legs and pelvis kept in maximal elevation for 24 hours after the injection. This is also a highly satisfactory treatment for the frequent priapism. The great drawback is its detrimental effect on a satisfactory automatic bladder. For this reason alcohol injection should be limited to the treatment of severe spasm and mass reflexes in the completely paraplegic patient who, even after one year, has shown no functional return, and whose bladder is either atonic with excessive residual urine or hypertonic with a small capacity. Whenever a spinal block, possibly due to a localized arachnoiditis, complicates the condition, laminectomy or revision of the extramedullary tissue lesion is indicated. Conservative treatment of muscle spasm involves the prevention of all irritating stimuli which initiate these reflex spasms, a task which in view of the very nature of the condition we must deal with is well nigh impossible. Large doses of phenobarbital, 0.2 to 0.3 gm, deserve a trial. The use of the galvanic alternating electric current, by which a tetanic muscle contraction from the anode is preferred, may be given a chance, but it will usually fail to accomplish spasm relief. Peripheral nerve surgery is employed with good results only for the adductor spasms, where section of the obturator nerves often leads to considerable improvement. Once contractions resistant to conservative physiotherapy have developed, and hope for functional improvement has been abandoned, orthopedic surgery may still contribute to getting a patient on his feet.

The rehabilitation program of paraplegics

hospitals General practitioners in charge of individual cases will profit much by following the principles of this treatment and by securing not only the co-operation of trained physiotherapists and nurses but also the active co-operation of the patients themselves (The reader is referred to the articles on rehabilitation by H A Rusk and by C G Deaver listed among the References for this section) Evaluation of the disability best done by a neurologist should precede the choice of treatment which should include physical and occupational therapy and the physical mental social psychologic and vocational adjustment of the patient to his handicapped condition Physical therapy started as early as possible should be directed toward improvement of voluntary muscle function and co-ordination of movements toward prevention or correction of contractures and toward stimulation of circulation and of general body functions Aside from the special therapeutic measures already mentioned massage and both active and passive motions should be carried out several times daily and may possibly be combined with various heat applications under water exercises and systematic muscle re-education Occupational therapy through carefully chosen activities has for its purpose the strengthening of weak muscles and the achievement of whatever use the patient can make of his paretic or paralyzed extremity Exercise and training of such muscles as were spared by the paralysis are particularly important In cases of injury or disease of the spine exercise must be postponed until the spine has become stable but after that the patient should be urged to move about in his bed to sit up to get on a chair etc Adaptive splints and other devices are necessary to help the patient use his extremities to stand up and finally to move about as much as he can A patient who is able to move his extremities under water and to swim will eventually be able to walk with the help of crutches and braces These mechanical appliances should be ordered and fitted by an orthopedist and where braces of the legs extend above the knee

surgical shoes should also be worn by the patient

The final stage in the treatment of paraplegics is reached with the integration of the patient into some kind of useful existence Psychologic stimulation to this end is necessary and much responsibility rests on the physician and his helpers

Patients with complete transverse lesions of the spinal cord especially those with interruption of continuity at a high segmental level remain sensitive with regard to all vegetative functions L F Pollock and his co-workers have demonstrated the lability of the blood pressure temperature regulation and urinary output all of which present functional deviations which deserve watching in these patients

Complications in paraplegics may be difficult to diagnose when they occur in anesthetic parts of the body and they may be of serious consequence in the case of intra-abdominal disease Many paraplegics seem to be hypersensitive to the sulfonamides Osteomyelitis soft tissue abscesses and em-

helpful in the prevention of embolism in the presence of thromboses of the deep veins Chronic rectal complaints associated with hemorrhages venous thrombosis formation of fistulas and fissures and prolapse of the rectum are frequent complications in cases of flaccid paralysis of the rectum and are often resistant to treatment

FREDERICK HILLER

REFERENCES

Bumpus H C Nourse M H and Thompson C

Deaver C G Evaluation of Disability and Rehabilitation Procedures of Patients with Spinal Cord

Rusk H A Rehabilitation JAMA 140 256 1949

NEURITIS AND BELL'S PALSY

Neuritis Treatment of neuritis is treatment of the great number of disturbances and diseases in which toxic, infectious, or degenerative lesions of the peripheral nerves play a more or less important role. Frequently also included in the clinical syndrome, "neuritis," are the manifold traumatic nerve lesions and those cases of symptomatic neuralgia, which, accompanied by motor and sensory disturbances, e.g., those affecting branches of the sciatic nerve, are the result of a compression or irritation of nerve roots. In many instances the attending physician is able to find and to eliminate the damaging agent or condition, and, by so doing, will be applying the most successful treatment for the given type of neuritis. This holds true, particularly, for the neuritis caused by external poisons and by deficiency and metabolic disorders, as well as for the traumatic (or mechanical) types of the disease. In other cases, the general examination will reveal an acute or chronic infectious or toxic disease with the neuritis presenting only one of many manifestations. Here the neuritis often outlasts other characteristic signs of the disease, as in diphtheria, for instance, and the physician would like to know what to do about it, and how to help the damaged nerves regain their functions. This very same question arises, of course, in another neuritic group, the one usually called "idiopathic polyneuritis," where exclusively nerve functions are damaged and where one obviously has to deal with an infectious or toxic agent, the affinity of which is limited or predominantly directed to the peripheral nerves or nerve roots, as in the Guillain Barre syndrome.

GENERAL TREATMENT Management of the more acute phases of a toxic, infectious polyneuritis, with or without fever, consists of bed rest and warmth. Heat is best applied locally in the form of hot packs or simply by the use of hot water bottles or electric pads under sufficient blankets. If the legs only are involved, radiant heat from an electric arc is useful. Heat usually has a soothing effect on the pain, but should not be overdone, nor an erythematous reaction of the skin is all that is necessary. Many recommend the use of mud packs (*fango*), sand baths, dia-

thermy, infra-red rays, etc. All are useful in so far as they cause an arterial hyperemia without weakening the patient by too much perspiration. Diaphoresis, using large amounts of hot fluids (lemonade, milk, or tea), sodium salicylate (1 to 2 gm.), and a general wet pack, is an old, sanctioned treatment in cases where the general circulatory condition, especially, permits such a drastic procedure. It is also customary to give potassium iodide (about 0.3 to 1.0 gm. three times daily, in enterically coated form) during the first week or two, and, if the patient shows no undesirable reaction, even to increase this dose until the nasal mucous membranes begin to show hypersecretion. Sulfonamides, which of themselves occasionally produce neuritic reactions, are not recommended, but penicillin may be tried. A total dose of about 10,000,000 units appears indicated in conditions which suggest an infectious etiology. Aureomycin and chloromycetin, which may prove to be even more efficacious, still await trial. Streptomycin's toxicity for the nervous tissues requires an absolute contraindication to its use.

LOCAL TREATMENT Local treatment of a painful neuritic condition employs hyperemia, not only by means of heat, but also by means of various rubefacient drugs, most of which are applied in the form of ointments. Iontophoresis, whereby certain drugs are introduced into the body through the intact skin with the help of a galvanic current, has never become popular, and it appears doubtful whether, for instance, the use of a 2 per cent aqueous histamine solution applied from the anode, has a better vasodilating effect than the external application of a histamine containing ointment over a diseased nerve. Other ointment ingredients which have a counterirritant effect, are methyl salicylate, eucalyptol, thymol, menthol, and methacholine. Rubefacients, which had already proved their usefulness in our grandmothers' time, are liquor ammonii caustici usually applied as linimentum ammoniacum, and chloroform which, combined with *oleum terebinthinae*, is gently massaged into the skin. After application of a counterirritant, wrapping the painful extremity in cotton often sustains the beneficial effect. The use of electric current during the acute stage of a neuritis is not recommended.

not even the "anodal galvanization" Mas sage, if used at all, should be applied only in the most gentle fashion

should be given preference over aminopyrine and phenacetin, which when given too long and in too large doses, may have unpleasant toxic side effects Morphine, codeine and other narcotics should be withheld as long as possible, and then be given only under strict supervision and for a limited time

during the day or in greater doses for the night Most neuritic pains disturb the patients sleep, and for this reason lower his threshold to pain

VITAMINS have attained an important place in the treatment of neuritis since the role of vitamin B₁ (thiamine) deficiency in the neuropathic manifestations in pellagra and its decisive curative effect on the peripheral neuritis in beriberi have become known We have gained the impression that an acute or an untreated case of polyneuritis, be it toxic infectious or of a clearly vitamin deficiency character, should receive thiamine chloride intramuscularly or intravenously in large doses After an intradermal test to rule out a possible individual hypersensitivity, 50 mg are given twice daily for about one week To use still larger doses may be indicated in desperate cases Ordinarily the patient will then be saturated with thiamine by the end of the first week, and should continue on oral thiamine, of which 10 to 20 mg daily will be ample The effect of thiamine is definitely enhanced by adding to it the other vitamins of the B complex This can be done properly by giving large amounts of brewers' yeast (50 to 60 gm per day) or the equivalent in the form of one of the many vitamin B or multivitamin preparations on the market Aside from thiamine (20 mg), such preparations should contain in one capsule niacin (50 to 100 mg), riboflavin (5 to 10 mg), pyridoxine (0.5 to 1.0 mg), and calcium pantothenate (1 to 5 mg), as well as vitamin C (50 to 100 mg)

Muscular Paralysis Treatment of muscular paralysis caused by peripheral neuritis demands particular attention The functional restitution of muscular power depends not only on the sufficient reinnervation of a muscle but also, especially in chronic cases, on the condition of the paralyzed muscles themselves It is generally understood that paralyzed muscles should not be kept in a state of prolonged tension and pull but it is equally important to prevent, if possible, a lasting complete relaxation of weakened muscles Muscular atrophy occurs rapidly, even in normal muscles, if the muscle is kept for any length of time in a state of complete inactivity, i.e., if its points of fixation remain maximally approximated Therefore, the position of a paretic extremity must be carefully watched A footboard or a posterior leg splint will serve to prevent a foot drop, and a rolled blanket under the knees for a few hours daily will keep the quadriceps from remaining in a state of continuous relaxation Even more important is skilled muscle reeducation for the prevention of deformities and contractures Massage and both passive and active motion are applied according to the principles discussed in the section on Infantile Paralysis Electric current for the purpose of muscle contraction may be applied where no active motion is possible It stands to reason that faradization can be useful only in muscles which react to this current, which, in other words, do not show a degenerative reaction In the presence of interrupted innervation only galvanic stimulation with a current sufficient to produce a good muscle contraction makes sense Smaller muscles are more easily treated than large ones, in which a tolerable stimulus often produces only partial contractions To be successful galvanization should be done duly in a systematic fashion (for instance, 20 to 30 contractions a minute for 3 to 5 minutes twice daily) Galvanization helps to retard the wasting of denervated muscles and appears to be particularly indicated when reinnervation will probably take place Strychnine, usually administered as strychnine hydrochlorate, 5 to 20 drops by mouth (increasing day by day) is an old remedy in polyneuritis, but probably does not have more than a general tonic effect

Complications in polyneuritis may arise from paralyses affecting cranial nerves the phrenic or the innervation of the bladder. The application of artificial respiration and the cure of a paralyzed bladder is described elsewhere in this book.

Bell's Palsy Treatment of Bell's palsy follows the same general principles as outlined above if the facial paralysis is of the so called "rheumatic or idiopathic" type. One often has the impression that large doses of salicylates and an intensive diaphoresis in the earliest stage have a prompt effect on the paralysis. In subacute or chronic cases slight massage of the face, galvanization and once traces of active motion appear reeducation of the facial musculature by regular exercises before a mirror are necessary. Statements made above concerning electrotherapy hold true for facial musculature also. The very fact that about 75 per cent of cases of Bell's palsy recover spontaneously makes it imperative that the paralyzed facial muscles be protected from unnecessary wast

alvanization

alyzed face

of the gen

erally used "hook in the corner of the mouth attached by a rubber sling to the ear" as being worse than useless may be somewhat exaggerated but his recommendation to support the face by strips of rigid adhesive tape which is not stuck to the paralyzed parts deserves to be followed. For the paralyzed orbicularis oculi he describes a support composed of two adhesive strips 1 cm. in width which keeps the lid in apposition to the eye so as to prevent an epiphora and which counteracts the weight of the paralyzed cheek thus preventing an ectropion. This support must be applied as early as possible.

Surgery consisting of nerve suture as an early treatment in facial paralysis is indicated only in mechanical injury to the nerve where anatomic interruption has been ascertained. Where a simple nerve suture is unfeasible owing to extensive nerve destruction the nerve ends may be united by means

serve a relatively normal appearance of the face provided the grafting is done early enough before the muscles are stretched too much.

Surgery in ordinary Bell's palsy will have to be considered in the smaller number of cases which show no return of function and after a number of months still present a degenerative reaction. Tickle recommends operation before the end of 6 months but he discourages it once the galvanic muscle

is of uncertain prognostic value and should not be taken as proof of an existing or impending denervation. One sees facial palsies where a surprisingly rapid functional restitution occurs in spite of a temporary loss of faradic muscle response. Operative technique used in chronic cases of ordinary Bell's palsy consists in uncovering of the facial nerve from the foramen stylomastoideum if necessary up to the horizontal semicircular canal followed by slitting of the nerve sheath. Tickle has also employed grafts (using the cutaneous femoris) with satisfactory results.

Treatment of otitic facial palsy belongs in the hands of an otologist but the general practitioner also will benefit from knowing and applying certain rules which have proved their value. Whether caused by contact infection, compression of the nerve by distended hyperemic blood vessels accompanying the nerve, a lymphangitis in the nerve canal or a nutritional disturbance of the nerve (K. Brunner) facial palsy in acute otitis media usually subsides under adequate treatment of the otitis usually with sulfa or antibiotic therapy. In a case of chronic otitis media facial palsy calls for a mastoidectomy. A palsy occurring during an operation on the ear asks for immediate decompression of the nerve whereas a palsy occurring postoperatively may disappear after removal of the tamponade from the wound (Kettel).

Too many people suffer from the disfigurement of a lasting facial paralysis. It is the author's impression that an active therapeutic attitude has been retarded by the anastomosis technique mentioned above which has been known and practiced for 70 years.

call for plastic facial surgery using fascial lata grafts, temporal or masseter muscle strips or tantalum wire which help to pre-

but which has always been unsatisfactory owing to the lack of emotional muscle response and to unpleasant associated movements in other muscle groups (shoulder, neck, and tongue). It would seem that otologists, familiar with the minute technique of operations on and about the ear, would find

have much better chances in facial than in peripheral nerve surgery in general

FREDERICK HILLER

REFERENCES

- Pickenil H P, and Pickenil, C M Early Treatment of Bell's Palsy *British M J*, 2 457, 1945
 Tickle T G Surgery of the Facial Nerve in 300 Operated Cases *Laryngoscope*, 55 191, 1945

MÉNIÈRE'S SYNDROME

The treatment of the condition known as Ménière's disease or syndrome or symptom complex has become more efficacious during the last decade as progress has been made in understanding its complicated etiology. The diagnosis is not difficult if it concerns only the syndrome of paroxysmal vertigo, tinnitus, and perception deafness, associated with severe nausea and vomiting, and further characterized by acute episodes with exacerbation of symptoms. As a rule the abnormal vestibular and cochlear manifestations are unilateral, but occasionally they may also affect the other ear.

One may assume that in a large number of cases a sudden increase of endolymphatic pressure precipitates the acute clinical attack. The cause of this sudden hydropic pressure varies from case to case. Mygind and Dederding attributed it to a disturbance of water and salt metabolism, but, as far as water metabolism, sodium retention, and serum potassium level are concerned, Talbott and Brown failed to show any significant deviations from normal in their cases. Yet low sodium diet and dehydration are often helpful, and it remains undecided whether this is due to alteration in the normal sodium-potassium relationship (Talbott and Brown) or whether this diet affects the electrolyte concentration and the hydration state of the tissues without producing a similar measurable effect in the blood.

Treatment of Ménière's syndrome is still not successful in all cases, in spite of various often helpful therapeutic approaches. Fortunately the vertigo not infrequently disappears spontaneously, or at least the vertigo-free intervals increase so that a marked improvement results. The gradual diminution of hearing is usually but not always accompanied by a lessening of the vertigo attacks. Loss of vestibular function in the affected ear may be followed by cessation of the attacks, but in a larger group of cases Walsh and Adson found that this is not the rule.

Any kind of medical treatment of Ménière's syndrome depends on the occupation, intelligence, social status, and psychologic attitude of the patient. These patients are usually extremely fearful and apprehensive, and need reassurance, which is often best achieved by explaining to them the true nature of their illness. Promises as to the cure of their condition should be avoided, but they should be told that with their cooperation the dreaded attacks of vertigo may be overcome.

Low sodium diet and dehydration (Mygind and Dederding) is one of the best means of treating these patients for any length of time. Dehydration is carried out after the patient has been subjected to a water retention test. With a normal fluid output, fluid intake should be restricted to 1000 cc or possibly less, whereas with a measurable water retention, fluid intake should be further reduced to accord with the extent that water is retained. To start this treatment properly, the patient is best hospitalized, or at least kept under strict observation at home, for approximately 1 or 2 weeks. Any therapeutic procedure which improves the general circu-

brushing, etc., is recommended. Artificial perspiration may have a good effect. A diet sufficiently low in sodium should consist of ingredients with naturally low sodium content, and no table salt should be used in the preparation of the food. This diet does not need to be meat-free, but milk and milk products should be restricted. Unsalted butter and bread must be used. Diet charts will help both physician and patient to avoid certain vegetables and to compose the right

Complications in polyneuritis may arise from paralysis affecting cranial nerves the phrenic or the innervation of the bladder. The application of artificial respiration and the cure of a paralyzed bladder is described elsewhere in this book.

Bell's Palsy: Treatment of Bell's palsy follows the same general principles as outlined above if the facial paralysis is of the so called "rheumatic" or "idiopathic" type. One often has the impression that large doses of salicylates and an intensive diaphoresis in the earliest stage have a prompt effect on the paralysis. In subacute or chronic cases

exercises before a mirror are necessary. Statements made above concerning electrotherapy hold true for facial musculature also. The very fact that about 75 per cent of cases of Bell's palsy recover spontaneously makes it imperative that the paralyzed facial muscles be protected from unnecessary wasting. Aside from faradization or galvanization a mechanical support of the paralyzed face is indicated. Pickerill's criticism of the generally used hook in the corner of the mouth attached by a rubber sling to the ear as being worse than useless may be somewhat exaggerated but his recommendation to support the face by strips of rigid adhesive tape which is not stuck to the paralyzed parts deserves to be followed. For the paralyzed orbicularis oculi he describes a support composed of two adhesive strips 1 cm. in width which keeps the lid in apposition to the eye so as to prevent an epiphora and which counteracts the weight of the paralyzed cheek thus preventing an ectropion. This support must be applied as early as possible.

Surgery consisting of nerve suture as an early treatment in facial paralysis is indicated only in mechanical injury to the nerve where anatomic interruption has been ascertained. Where a simple nerve suture is unfeasible owing to extensive nerve destruction the nerve ends may be united by means of a graft or less advantageously anastomosis with either the accessory or the hypoglossus nerve may be considered. Certain injuries call for plastic facial surgery using fascial grafts temporal or masseter muscle strips or tantalum wire which help to pre-

serve a relatively normal appearance of the face provided the grafting is done early enough before the muscles are stretched too much.

Surgery in ordinary Bell's palsy will have to be considered in the smaller number of cases which show no return of function and after a number of months still present a degenerative reaction. Tickle recommends operation before the end of 6 months but he discourages it once the galvanic muscle

is of uncertain prognostic value and should not be taken as proof of an existing or impending denervation. One sees facial palsies where a surprisingly rapid functional restitution occurs in spite of a temporary loss of faradic muscle response. Operative technique used in chronic cases of ordinary Bell's palsy consists in uncovering of the facial nerve from the foramen stylomastoideum if necessary up to the horizontal semicircular canal followed by slitting of the nerve sheath. Tickle has also employed grafts (using the iliac cutaneous femoris) with satisfactory results.

Treatment of otitic facial palsy belongs in the hands of an otologist but the general practitioner also will benefit from knowing and applying certain rules which have proved their value. Whether caused by contact infection compression of the nerve by distended hyperemic blood vessels accompanying the nerve a lymphangitis in the nerve canal or a nutritional disturbance of the nerve (A. Brunner) facial palsy in acute otitis media usually subsides under adequate treatment of the otitis usually with sulfa or antibiotic therapy. In a case of chronic otitis media facial palsy calls for a mastoidectomy. A palsy occurring during an operation on the ear risks for immediate decompression of the nerve whereas a palsy occurring postoperatively may disappear after removal of the tamponade from the wound (Kettel).

Too many people suffer from the disfigurement of a lasting facial paralysis. It is the author's impression that an active therapeutic attitude has been retarded by the anastomosis technique mentioned above which has been known and practiced for 70 years.

but which has always been unsatisfactory owing to the lack of emotional muscle response and to unpleasant associated movements in other muscle groups (shoulder, neck, and tongue). It would seem that otologists, familiar with the minute technic of operations on and about the ear, would find

have much better chances in facial than in peripheral nerve surgery in general

FREDERICK HILLER

REFERENCES

- Pickenil H P, and Pickenil C M Early Treatment of Bell's Palsy *British M J* 2 457 1945
 Tickle T G Surgery of the Facial Nerve in 300 Operated Cases *Laryngoscope* 55 191, 1945

MENIERE'S SYNDROME

The treatment of the condition known as Meniere's disease or syndrome or symptom complex has become more efficacious during the last decade as progress has been made in understanding its complicated etiology. The diagnosis is not difficult if it concerns only the syndrome of paroxysmal vertigo, tinnitus and perception deafness associated with severe nausea and vomiting, and further characterized by acute episodes with exacerbation of symptoms. As a rule the abnormal vestibular and cochlear manifestations are unilateral, but occasionally they may also affect the other ear.

One may assume that in a large number of cases a sudden increase of endolymphatic pressure precipitates the acute clinical attack. The cause of this sudden hydropic pressure varies from case to case. Mygind and Dederding attributed it to a disturbance of water and salt metabolism but, as far as water metabolism, sodium retention and serum potassium level are concerned, Talbott and Brown failed to show any significant deviations from normal in their cases. Yet low sodium diet and dehydration are often helpful, and it remains undecided whether this is due to alteration in the normal sodium-potassium relationship (Talbott and Brown) or whether this diet affects the electrolyte

Treatment of Meniere's syndrome is still not successful in all cases in spite of various often helpful therapeutic approaches. Fortunately the vertigo not infrequently disappears spontaneously, or at least the vertigo-free intervals increase so that a marked improvement results. The gradual diminution of hearing is usually but not always accompanied by a lessening of the vertigo attacks. Loss of vestibular function in the affected ear may be followed by cessation of the attacks, but in a larger group of cases Walsh and Adson found that this is not the rule.

Any kind of medical treatment of Meniere's syndrome depends on the occupation, intelligence, social status, and psychologic attitude of the patient. These patients are usually extremely fearful and apprehensive, and need reassurance, which is often best achieved by explaining to them the true nature of their illness. Promises as to the cure of their condition should be avoided, but they should be told that with their co-operation the dreaded attacks of vertigo may be overcome.

Low sodium diet and dehydration (Mygind and Dederding) is one of the best means of treating these patients for any length of time. Dehydration is carried out after the patient has been subjected to a water retention test. With a normal fluid output, fluid intake should be restricted to 1000 cc or possibly less, whereas with a measurable water retention, fluid intake should be further reduced to accord with the extent that water is retained. To start this treatment properly, the patient is best hospitalized, or at least kept under strict observation at home, for approximately 1 or 2 weeks. Any therapeutic procedure which improves the general circu-

brushing, etc., is recommended. Artificial perspiration may have a good effect. A diet sufficiently low in sodium should consist of ingredients with naturally low sodium content, and no table salt should be used in the preparation of the food. This diet does not need to be meat free, but milk and milk products should be restricted. Unsalted butter and bread must be used. Diet charts will help both physician and patient to avoid certain vegetables and to compose the right

Complications in polyneuritis may arise from paralyses affecting cranial nerves the hrenic or the innervation of the bladder the application of artificial respiration and the cure of a paralyzed bladder is described elsewhere in this book.

Bell's Palsy Treatment of Bell's palsy follows the same general principles as outlined above if the facial paralysis is of the so called "rheumatic" or "idiopathic" type. One often has the impression that large doses of salicylates and an intensive diaphoresis in the earliest stage have a prompt effect on the paralysis. In subacute or chronic cases slight massage of the face galvanization and once traces of active motion appear re-education of the facial musculature by regular exercises before a mirror are necessary.

Statements made above concerning electrotherapy hold true for facial musculature also. The very fact that about 75 per cent of cases of Bell's palsy recover spontaneously makes it imperative that the paralyzed facial muscles be protected from unnecessary wasting. Aside from faradization or galvanization a mechanical support of the paralyzed face is indicated. Pickersill's criticism of the generally used "hook in the corner of the mouth attached by a rubber sling to the ear," as being worse than useless may be somewhat exaggerated but his recommendation to support the face by strips of rigid adhesive tape which is not stuck to the paralyzed parts deserves to be followed. For the paralyzed orbicularis oculi he describes a support composed of two adhesive strips 1 cm. in width which keeps the lid in apposition to the eye so as to prevent an epiphora and which counteracts the weight of the paralyzed cheek thus preventing an ectropion. This support must be applied as early as possible.

Surgery consisting of nerve suture as an early treatment in facial paralysis is indicated only in mechanical injury to the nerve where anatomic interruption has been ascertained. Where a simple nerve suture is unfeasible owing to extensive nerve destruction the nerve ends may be united by means of a graft or less advantageously anastomosis with either the accessory or the hypoglossus nerve may be considered. Certain injuries call for plastic facial surgery, using fascia lata grafts temporal or masseter muscle strips or tantalum wire which help to pre-

serve a relatively normal appearance of the face, provided the grafting is done early enough before the muscles are stretched too much.

Surgery in ordinary Bell's palsy will have to be considered in the smaller number of cases which show no return of function and after a number of months still present a degenerative reaction. Tickle recommends operation before the end of 6 months but he discourages it once the galvanic muscle response has disappeared. It should be stressed that the disappearance of the muscular contraction on faradic stimulation alone is of uncertain prognostic value and should not be taken as proof of an existing or impending denervation. One sees facial palsies where a surprisingly rapid functional restitution occurs in spite of a temporary loss of faradic muscle response. Operative technique used in chronic cases of ordinary Bell's palsy consists in uncovering of the facial nerve from the foramen stylomastoideum if necessary up to the horizontal semicircular canal followed by slitting of the nerve sheath. Tickle has also employed grafts (using the cutaneous femoris) with satisfactory results.

Treatment of otitic facial palsy belongs in the hands of an otologist but the general practitioner also will benefit from knowing and applying certain rules which have proved their value. Whether caused by contact infection compression of the nerve by distended hyperemic blood vessels accompanying the nerve a lymphangitis in the nerve canal or a nutritional disturbance of the nerve (A. Brunner) facial palsy in acute otitis media usually subsides under adequate treatment of the otitis usually with sulfa or antibiotic therapy. In a case of chronic otitis media facial palsy calls for a mastoidectomy. A palsy occurring during an operation on the ear asks for immediate decompression of the nerve whereas a palsy occurring postoperatively may disappear after removal of the tamponade from the wound (Kettel).

Too many people suffer from the disfigurement of a lasting facial paralysis. It is the author's impression that an active therapeutic attitude has been retarded by the anastomosis technique mentioned above which has been known and practiced for 70 years.

but which has always been unsatisfactory owing to the lack of emotional muscle response and to unpleasant associated movements in other muscle groups (shoulder, neck, and tongue). It would seem that otologists, familiar with the minute technique of operations on and about the ear, would find it relatively easy to approach the facial nerve directly, particularly above its exit through the styloid foramen. Autologous grafts may have much better chances in facial than in peripheral nerve surgery in general.

FREDERICK HILLER

REFERENCES

- Pickenll H P, and Pickenll C M Early Treatment of Bell's Palsy *British M J* 2:457 1945
 Tickle, T G Surgery of the Facial Nerve in 300 Operated Cases *Laryngoscope* 55:191, 1945

MENIERE'S SYNDROME

The treatment of the condition known as Menière's disease or syndrome or symptom complex has become more efficacious during the last decade as progress has been made in understanding its complicated etiology. The diagnosis is not difficult if it concerns only the syndrome of paroxysmal vertigo, tinnitus, and perception deafness associated with severe nausea and vomiting, and further characterized by acute episodes with exacerbation of symptoms. As a rule the abnormal vestibular and cochlear manifestations are unilateral, but occasionally they may also affect the other ear.

One may assume that in a large number of cases a sudden increase of endolymphatic pressure precipitates the acute clinical attack. The cause of this sudden hydrostatic pressure varies from case to case. Mygind and Dederding attributed it to a disturbance of water and salt metabolism, but, as far as water metabolism, sodium retention, and serum potassium level are concerned Talbott and Brown failed to show any significant deviations from normal in their cases. Yet low sodium diet and dehydration are often helpful, and it remains undecided whether this is due to alteration in the normal sodium potassium relationship (Talbott and Brown) or whether this diet affects the electrolyte concentration and the hydration state of the tissues without producing a similar measurable effect in the blood.

Treatment of Meniere's syndrome is still not successful in all cases, in spite of various often helpful therapeutic approaches. Fortunately the vertigo not infrequently disappears spontaneously, or at least the vertigo-free intervals increase so that a marked improvement results. The gradual diminution of hearing is usually but not always accompanied by a lessening of the vertigo attacks. Loss of vestibular function in the affected ear may be followed by cessation of the attacks, but in a larger group of cases Walsh and Adson found that this is not the rule.

Any kind of medical treatment of Meniere's syndrome depends on the occupation, intelligence, social status, and psychology of the patient. These patients are usually extremely fearful and apprehensive, and need reassurance, which is often best achieved by explaining to them the true nature of their illness. Promises as to the cure of their condition should be avoided, but they should be told that with their cooperation the dreaded attacks of vertigo may be overcome.

Low sodium diet and dehydration (Mygind and Dederding) is one of the best means of treating these patients for any length of time. Dehydration is carried out after the patient has been subjected to a water retention test. With a normal fluid output, fluid intake should be restricted to 1000 cc. or possibly less, whereas with a measurable water retention, fluid intake should be further reduced to accord with the extent that water is retained. To start this treatment properly, the patient is best hospitalized, or at least kept under strict observation at home, for

brushing, etc., is recommended. Artificial perspiration may have a good effect. A diet sufficiently low in sodium should consist of ingredients with naturally low sodium content, and no table salt should be used in the preparation of the food. This diet does not need to be meat free, but milk and milk products should be restricted. Unsalted butter and bread must be used. Diet charts will help both physician and patient to avoid certain vegetables and to compose the right

kind of meals Salt substitutes may be used neocurtisal or cosalt being most useful In themselves they constitute the essentials of the treatment recommended by Furstenberg and by Talbott and Brown In our experience such large doses of ammonium chloride as Furstenberg recommends i.e. 9 gm daily for 3 days followed by a salt free diet for 2 days and continued in this way eventually and all too frequently cause unpleasant reactions such as nausea vomiting itching constipation and general weakness But smaller amounts are well taken for long periods The intake of this salt may be increased during relapses of vertigo The same thing is to be said concerning potassium chloride which Talbott and Brown have recommended in daily doses of 6 to 10 gm in aqueous solution It is true that potassium chloride is better tolerated than is potassium nitrate (Walsh and Adson) which most patients refuse to take for long periods but whether it has any specific action or merely acts first of all and possibly only as a diuretic is debatable The more chronic the cases of Ménière's syndrome the more must one adapt the treatment to what is compatible with a comparatively normal life These requirements are fulfilled by a low salt diet combined with a low fluid intake at a tolerable minimum and particularly in recurrent episodes of vertigo by the addition of about 5 gm daily of potassium chloride which the patient may use in crystal form in a salt shaker

Mercurials as diuretics may be tried in a particularly severe case but should not be repeated beyond the acute stage Regular bowel movements are necessary and non sodium laxatives are often indicated in order to accelerate dehydration The patient's basal metabolic rate should be determined and thyroid given as needed This may be a decisive factor in the process of tissue dehydration It goes without saying that sodium bicarbonate sodium bromide or any waters containing sodium are strictly forbidden

In patients with obvious vasomotor instability particularly in the presence of vasospastic phenomena elsewhere in the body (see above) and also in patients who do not react promptly to dehydration the administration of histamine as em-

ployed by Sheldon and Horton should be tried Histamine acid phosphate 10 mg in 20 cc normal saline (or 0.8 per cent potassium chloride solution) given over a period of 1 to 1½ hours occasionally controls the acute symptoms of an attack It may be repeated once or twice the following days and if necessary can be given even for weeks Subcutaneous or intramuscular maintenance injections are preferable For the continuous treatment of these vasomotor disturbances the use of papaverine hydrochloride in tablets or capsules 0.1 gm combined with nicotinic acid in tablets of 50 mg three times daily is often beneficial This treatment should be kept up for months and reduced only gradually Nicotinic acid 25 mg intramuscularly as advised by Atkinson usually gives no better results

The tinnitus and the deafness improve occasionally under any treatment that affects the vertigo especially when the treatment is begun early enough However the majority of patients continue to suffer from their ear noises finding relief only by personal adjustment to this disagreeable symptom Even more patients fail to show any improvement in their deafness or in their distorted hearing, a feature that tends to grow worse with time Patients with evidence of a bilateral labyrinthine disturbance usually react less well to any kind of medical treatment

Many patients are so emotionally disturbed during acute attacks of vertigo or in anticipating relapses of their misery that sedation best combined with small doses of hyoscine may be necessary Others will have to be advised to restrict their activities at least for some time or even to make a change of occupation if sudden vertigo should mean great danger to themselves or to others Unless the disease has been controlled for many months patients suffering from Ménière's syndrome should not be permitted to drive a car

Surgery as treatment for the syndrome should be reserved for those rare patients who do not respond to any kind of medical treatment Frazier and Dandy have shown that intracranial severance of the eighth nerve is followed by "cure of the disease" Yet there are not a few instances where symptoms so abolished later appeared on the other side Portman's operation i.e. dram

DISEASES OF THE NERVOUS SYSTEM

age of the labyrinth through the sacculus en-
dolympathicus in the posterior cranial fossa
though acclaimed by some is criticized by
others Destruction of the labyrinth or of a
small portion of the semicircular canals ap-
pears to be a simpler and quite satisfactory
method although tinnitus may sometimes
persist The method used will have to be left
to the surgeon—subtemporal destruction
(Putnam) injection of alcohol into the ex-
ternal semicircular canal (Mollison) coagu-
lation of the whole or a part of the end-organ
(Day), or the much less harmful and rather
conservative procedure recommended by
Cawthorne and Hallpike who remove a
piece of the membranous external semicircu-
lar canal or simply tear it across and who
observe that this will lead to abolition of the
vertigo but not of the hearing which to-
gether with the tinnitus may even show some
improvement Provided the other ear is nor-
mal loss of hearing through an operation is
not regarded as a contraindication to sur-
gery since the hearing in chronic cases of
Ménière's disease is usually so badly and
disturbingly affected that nothing is gained
by saving it

Surgical destruction of the labyrinth is
usually followed by an acute exacerbation
of the vertigo just as we see it in labyrinthine
injuries Rehabilitation after loss of one
labyrinth is a necessary procedure and should
start with preparing and training the patient
for the unpleasant consequences of the op-
eration The patient should be told that the
vertigo will disappear in time and that physi-
cal exertion will be followed by easy fatiga-
tion which may last for months After the
operation physical exercises combined with
constant encouragement should be started
as soon as possible The patient begins with
head movements first with the eyes
closed then with the eyes focused on near
objects Special attention
must be given to the retraining of the
sense of position in space of the head as
well as of the body and the extremities The
movements are speeded up gradually and
slow alternating movements must be prac-
ticed daily Within 2 weeks the patient
will be able to walk and with further
practice (turning stooping bending
up and down stairs etc) he will be able
to do light work by the end of a month

For a description of an elaborate and sys-
tematic rehabilitation procedure the reader must
consult Cooksey

Surgical removal of foci of infection after
failure of conservative treatment should be
dealt with in every case of Meniere's syn-
drome even though others have not achieved
Wright's excellent results with this as the
exclusive treatment

FREDERICK HILLER

REFERENCES

- Atkinson M Meniere's Syndrome Comparison of
Results of Medical and Surgical Treatment *Arch
Neurol & Psychiat* 5 192 1945
Atkinson M Meniere's Syndrome and Migraine
Observations on Common Causal Relationship
Ann Int Med 18 797 1943
Cawthorne T Meniere's Disease *Ann Otol Rhin
& Laryng* 56 18 1947
Cawthorne T Vestibular Injuries *Proc Roy Soc
Med* 39 270 1946
Cawthorne T and Hallpike C S Some re-
cent Work on Investigation and Treatment of
Ménière's Disease *Proc Roy Soc Med*, 36
533 1943
Cooksey F S Rehabilitation in Vestibular Injuries
Proc Roy Soc Med 39 273 1946
Dandy W E Meniere's Disease Its Diagnosis and
Method of Treatment *Arch Surg* 16 1127 1918
Day A M Surgery of Labyrinth for Meniere's Dis-
ease *Tr Am Acad Ophth* (1943) 48 221 1944
Frazier C H Intracranial Division of the Auditory
Nerve for Persistent Aural Vertigo *Surg Gynec
& Obst* 15 525 1912
Furstenberg A C Meniere's Symptom Complex
Medical Treatment *Tr Pacific Coast Oto-Ophth
Soc* 21 150 1938
Hagens C W Vertigo *Indust Med* 17 488 1948
Mollison W M Surgical Treatment of Vertigo by
Opening External Semicircular Canal and Inject-
ing Alcohol *Acta oto-laryng* 27 222 1939
Mygind S H and Dederding D Diagnosis and
Treatment of Meniere's Disease *Ann Otol Rhin
& Laryng* 47 783 1938
Putnam T J Treatment of Recurrent Vertigo
(Meniere's Syndrome) by Subtemporal Destruc-
tion of Labyrinth *Arch Otolaryng* 27 161 1938
Sheldon C H and Horton B T Treatment of
Meniere's Disease with Histamine Administered
Intravenously *Proc Staff Meet Mayo Clin* 15
17 1940
Talbot J H and Brown W R Meniere's Syn-
drome Acid base Constituents of the Blood
Treatment with Potassium Chloride *JAMA*,
114 125 1940
Walsh M N and Adson A W Meniere's Syn-
drome Medical vs Surgical Treatment. *JAMA*
114 130 1940
Wright, A J Further Clinical Observations on Na-
ture and Treatment of Meniere's Disease *Proc
Roy Soc Med* 33 459 1940

DISEASES OF THE SKIN

IMPETIGO CONTAGIOSA

This is a superficial type of pyoderma and may be produced by staphylococci or streptococci, more commonly by the former. It is highly contagious in the newborn, fairly contagious in young children, and only mildly so in adults. Infection is carried by the child's fingers, picking his nose or his cheeks.

The disease is characterized by heavy, "stuck on" crusts, and the first indication of treatment is the removal of these bulky crusts. This can be accomplished by thoroughly bathing them with a saturated solution of boric acid, then removing the crusts with sterile forceps, leaving a raw, oozing surface, which is then treated with an antiseptic ointment.

One of the best ointments is ammoniated mercury incorporated in a greaseless base. For children it is used in 3 per cent and for adults in 5 per cent strength. Unfortunately some children are allergic to mercury, and for those individuals a 2 to 3 per cent vioform (Giba) ointment may be used, or a 5 per cent penicillin ointment. Occasionally penicillin will irritate the skin if it is used longer than five days. If this, or any other of these ointments is too irritating the affected areas may be painted with a 2 per cent solution of gentian violet. This stains the skin a deep

and eradicate the disease. This treatment is not advisable for adults unless they are prepared to remain in seclusion.

Ointments should be rubbed into the affected areas several times during the day and always before retiring. The face should be washed twice a day at least, and men should shave every day. While shaving may irritate the raw areas, it keeps the skin cleaner and hastens recovery.

Inasmuch as the disease spreads by auto-inoculation, it is well to have the patient wear white cotton gloves at night. This lessens the danger of reinfection by scratching.

In years past the tendency has been to use ammoniated mercury in 10 per cent strength. This is too strong and may produce considerable dermatitis, 3 per cent is strong enough for children, and 5 per cent for adults. I have also found pragmasol ointment of value.

The disease may leave pink or red stains for a few days but no scars.

EDWARD A. OLIVER

ACNE

Acne is a disease of adolescence. Comedo formation and increased oiliness of the skin appear about the age of 12. The disease may begin at this age and last until the patient is 20.

The treatment is both general and topical. General measures consist of the correction of constipation if it is present, either by care

of water. While the diet is not actually responsible for acne, it does play an important role in its etiology, and for that reason the patient should avoid chocolate, cocoa, gravies, greasy foods, nuts, and too much milk and cream. Fatty foods, pastries, and creams also aggravate the disease. Uniodized salt should be recommended to these patients to take the place of the commonly used iodized variety.

The teeth should be examined carefully for abscesses, and the throat for signs of infection. If diseased teeth or tonsils are found, they should be removed.

Regular bathing is important, but hot baths should be avoided. Cold showers in the morning, followed by a vigorous rub

down, are beneficial, and do much to improve the general circulation

If the patient is anemic and underweight, suitable tonics containing liver and iron should be given

made in endocrinology, particularly in the preparation of anterior pituitary and male and female sex hormones, the hormonal treatment has as yet proved of little value

Vaccine treatment has not proved of much value, and most dermatologists have discontinued its use

Local Treatment The face should be washed thoroughly several times a day with a good toilet soap. In the case of extremely oily skins, tincture of green soap may be used. Cold cream must not be used. Comedones should be expressed with a comedo expressor several times a week. After bathing at night a sulfur lotion or ointment should be thoroughly applied to the skin and left on over night. I prefer lotions, and two of the most popular lotions I use are

(1) Sulfur precip	8
Pulv camphor	4
Acid salicylic	0.66
Tragacanth	0.66
Aqua dest ad	120
(2) Lotio Alba	
Zinc sulfate	4
Potassium sulfurette	4
Glycerin	II
Aqua dest ad	120

Lotions containing sulfur and resorcin are effective, though some patients may be allergic to resorcin. One of the best of these lotions which seldom if ever, produces much irritation, is sulforecin lotion (Texas Pharmacol Co.)

In obstinate cases with much pustulation and induration wet compresses of dilute Vlemunck's solution are effective. Vlemunck's solution is made up of calcs vivae—15 sulfur sublimata—30, aqua—300 cc. This is boiled down to 180 cc then filtered. One tablespoonful is diluted to a pint of warm water and warm wet compresses are applied for 30 minutes to an hour every night

In every case of acne the scalp should receive

careful attention. Most cases of acne are accompanied by an oily, scaling seborrhea of the scalp, and this of course should be treated, as well as the acne. For this the following ointment should be thoroughly rubbed into the scalp three times a week.

Sulfur precip	3
Acid salicylic	0.33
Greaseless base ad	30

Another excellent lotion that also may be used instead of an ointment is

Euresol pro capillis	6
Hydrarg bichloride	0.18
Spts formicari	30
Spts odorata	30
Spts vini rectif	70
Aqua dest ad	240

This should be carefully applied to the scalp three times a week using the tips of the fingers or a small cotton swab

Röntgen therapy is one of the most effective methods of treating acne, and for boys and girls 17 years of age and over, it is the treatment that offers the most speedy and permanent cure. I do not believe in its use for patients 16 years of age and younger. The treatment should be given only by a competent dermatologist well trained in roentgenotherapy. From eight to ten treatments of unfiltered therapy in doses of 75 r given once weekly to the affected areas, will effect marked improvement, and a permanent

duces the scars

Ultraviolet lamp therapy is often effective in milder cases, and may be used after the

and in that way lessening the amount of scarring that may appear in some cases

Acne Rosacea This affection is seen in older individuals. In contrast to acne vulgaris which affects the face, the chest back, and shoulders, acne rosacea affects the face only, chiefly the nose, but also the forehead, cheeks, and chin. The treatment of acne rosacea is both local and general. The local treatment recommended is the use of lotio alba, just mentioned under acne's treatment,

and wet compresses of Vlemmckx's solution. In stubborn cases a 40 per cent sulfur paste is of great value. The formula commonly used is

Sulfur precip	12
Ung petrolatum ad	30

This is not irritating, and is well tolerated by most patients.

General measures to be followed are the careful regulation of the diet. Anything which causes flushing or heating of the face, such as overindulgence in coffee tea, or alcohol, is to be avoided. Chocolate, highly seasoned foods, spicy foods, and fried foods are also taboo. Acne rosacea is seen commonly in women past the menopause, so it should be

and if present, and foci of infection in the teeth or tonsils should be removed.

For internal use I place a great deal of reliance on ketochol a bile acid salt. This is given in tablets—one tablet three times daily, after meals. In my experience with the use of lotio alba and ketochol I have had excellent results.

Vitamin B complex is highly recommended by many dermatologists, and dilute HCl in average doses also has been effective.

When and if the condition has progressed to the stage of rhinophyma, surgical measures are indicated. Surgeons remove these redundant masses of tissue with excellent results, by paring them down with a sharp scalpel. No skin grafting is necessary.

EDWARD A. OLIVER

MYCOSES OF THE HAIRLESS SKIN

Tinea Glabrosa (Ringworm of the Smooth Skin) Superficial fungous infections of the skin may occur as scaling lesions, circinate patches, solid plaques, or in gyrate configurations. Some cases may stimulate the eruptions of pityriasis rosea, seborrheic dermatitis or eczema, and for that reason treatment should not be begun until the

M lanosum The source of infection in this case is generally a stray kitten or some household pet which harbors the disease. Finding the source is then easy.

The most commonly used treatment is an ointment of ammoniated mercury of 5 per cent strength. Anointing the affected areas with this twice daily for a week or 10 days, will cause the lesions to disappear rapidly. Another ointment of value is one containing 3 per cent precipitated sulfur and 3 per cent salicylic acid, and still another, useful for the dry, scaling types, is

Acid salicylic	1
Acid benzoic	2
Ung aq rosae	15
Ung petrolatum	15

Patches that are moist and eczematous should be treated with soothing lotions such as calamine lotion, or with wet compresses of aluminum subacetate solution, diluted 1 oz to 1 pint of cool water, before receiving energetic treatment, and a valuable ointment if eczematization is present, is one containing equal parts of davalan ointment (crude coal tar ointment) and zinc oxide ointment. The disease responds to treatment.

Tinea Cruris This rather common dermatophytosis affects the inner and upper part of the thighs, and is commonly known as "gym itch," "dhubie itch," or eczema marginatum. It is caused by the *Epidermophyton inguinale*, and is generally contracted from wearing infected articles of clothing such as shorts, suspensories or jock straps.

The localization of the infection is the result of the predilection of the fungus for intertriginous areas. The same infection may occur in the axillae and about the anus.

If the skin is dry and scaling, as it generally is in epidermophyton infections, an ointment of 3 per cent precipitated sulfur and 3 per cent salicylic acid, rubbed into the affected areas once daily for a week or 10 days will readily effect a cure. Resorcinol, 10 per cent in a zinc oxide and lime water lotion will also cure it readily.

If, however, there is considerable inflammation present it is best to apply a 1 per cent aqueous solution of gentian violet until

may be found causing ringworm of the smooth skin the commonest of which is

it has cleared up. This is applied once daily with a cotton swab, for 3 or 4 days, and when the inflammation has subsided the sulfur and salicylic acid ointment may be used until all signs of the disease have disappeared.

Tinea Pedis (Ringworm of the Feet; "Athlete's Foot") This form of ringworm is so common that it has been estimated that from 50 to 90 per cent of the American public are afflicted with it sometime in their life.

There are two different forms of this disease, and each is quite different from the other in appearance, behavior and response to treatment.

TYPE 1 This is a moist inflammatory type, due to infection with *Trichophyton gypsum*. It is characterized by the development of vesicles and bullae on the soles and sides of the feet, by vesicular development on the toes and by maceration of the skin between the toes. Subsequent rupture of these vesicles and bullae sometimes leads to secondary infection.

Accompanying this type of infection, there is often an eruption of vesicles on the sides of the fingers and in the palms of the hands. These lesions are known as dermatophytids or "ids" and are the result of the dissemination of the products of fungi on the feet through the blood stream.

Inasmuch as this type is generally inflammatory when first seen the application of wet compresses or soaking the feet in anti-septic solutions is the treatment indicated. Before using these solutions the distended vesicles and bullae should be opened and the debris cut away.

The solutions most commonly used are aluminum subacetate solution diluted 1 oz to 1 pint of cool water, or a saturated solution of boric acid crystals in warm water and, if secondary infection is present, a solution of 0.25 to 0.5 per cent silver nitrate is of value.

In using compresses, the patient should be instructed to keep them wet, and applied constantly for the first day or two. After that he should use them two or three times a day for 20 to 30 minutes at a time.

For a foot bath nothing is better than a warm 1:3000 solution of potassium permanganate, in which the patient soaks his feet twice daily for 30 minutes.

As the inflammatory symptoms disappear,

ointments may be used. Desenex ointment, an undecylenic acid preparation, should be rubbed into the soles and between the toes, every night. Another valuable ointment is Whitfield's ointment in half strength, the formula for which is

Acid salicylic	1
Acid benzoic	2
Cold cream	15
Vaseline	15

This too should be thoroughly rubbed into the affected parts every night.

If there is no eruption on the soles and the infection consists only of maceration and vesiculation between the toes, painting these areas with a 2 per cent aqueous solution of gentian violet, a 1 per cent solution of iodine crystals in benzol or a 1 per cent solution of brilliant green will be beneficial.

In these acute cases roentgen therapy hastens recovery, 75 r of unfiltered radiation to the soles of the feet at weekly intervals for two to three treatments produces rapid involution of vesicles and bullae and shortens the course of the disease.

TYPE 2 This is a more chronic type, caused by *Trichophyton purpureum*. There is practically never any vesiculation or inflammatory reaction in this type. The plantar aspect of the feet is invariably involved, and the skin is dull red or brown in color, thickened, and the seat of a branny desquamation. Where the hands are involved the palms, dorsal surfaces, fingers, and fingernails are infected.

In this type of the disease, ointments are the treatment of choice. Full strength Whitfield's ointment of

Acid salicylic	2
Acid benzoic	4
Lanolin	15
Vaseline	15

is a valuable one and another that produces satisfactory results is anthralin ointment. Treatment should be commenced with a strength of 0.1 per cent, and if this produces no irritation it may be increased to 0.25 per cent.

It is the general belief that chronic cases are seldom cured, and that relapses after an apparent cure are more common than reinfections.

Certain hygienic rules should be applied to every patient with ringworm of the feet. The shoes, slippers, and other footwear should be sponged out each week with a 10 per cent solution of formaldehyde, and should not be worn again for 24 hours, in order that contact dermatitis from formaldehyde may be avoided.

Cotton socks should be boiled for 10 minutes or soaked for half an hour in a 1:1000 solution of bichloride of mercury before being washed in soap and water.

The bathtub used by a patient with dermatophytosis should be washed with a 1:1000 solution of bichloride or with a dilute solution of cresol and the bath mat should be used only by the infected person. He should wear paper slippers in walking to and from the bath. To avoid relapses or reinfection the patient should be told to dry his feet most carefully after bathing, paying particular attention to the interspaces between the toes. A dusting powder of 10 per cent sodium thiosulphate in talcum is an excellent preparation to use between the toes and on the soles of the feet daily.

Tinea Manuum (Ringworm of the Hands) This fortunately is not a common disease. In the acute inflammatory type of *tinea pedis* a dermatophytid eruption is common on the sides of the fingers and on the palms. This diagnosis should not be made unless there are active foci of infection on the feet from which mycelia have been recovered. If the diagnosis has been carefully made, a soothing lotion will suffice to dry up these secondary lesions, followed by the following ointment:

Ichthyol	0.66
Calamine	4
Zinc oxide	4
Cold cream ad	30

rubbed into the affected parts at night.

In the chronic cases caused by the *Trichophyton purpureum*, half strength Whitfield's ointment or 0.1 per cent anthralin ointment will be helpful in eradicating the dry, scaling patches.

EDWARD A. OLIVER

SCABIES

Since the end of the war, with the return of the troops, the incidence of scabies has

increased greatly. Not only did many soldiers return with it, but they infected their families on their return. In no other skin disease is the need for cleanliness greater. Previous to the introduction of the newer drugs in the last few years, sulfur was the drug of greatest value. No matter what drug is used the general instructions are the same.

(1) The patient is instructed to take a warm bath, scrubbing vigorously the wrists, the axillae, the hands, and the genitalia, for these are the common locations of the itch mite.

(2) After bathing the ointment, if it is a sulfur ointment, is thoroughly rubbed into the skin, from the neck to the soles of the feet.

(3) The patient changes the sheets and blankets on his bed, dons clean sleeping garments and clean underclothes the next day.

(4) He anoints himself well every night for 4 nights with this ointment, but does not take a bath until the morning of the fifth day.

(5) After this bath, he changes his under clothes, sheets, and night clothes, and stops treatment.

No treatment is given for a week but if the itching persists, he repeats the same course.

The formula we commonly use is:

Sulfur precip	6
Balsam of Peru	6
Sapo viridis	8
Petrolatum ad	120

This treatment is a valuable and reliable method of treating scabies, but it is messy and dirty, and the average patient does not like it.

In the last few years we have used the drug benzyl benzoate. This is diluted one half for use and the instructions given are the same as are used with the sulfur method of treatment, except that the patient, after taking a bath, applies the solution then allows it to dry for 10 to 15 minutes, then reapplies it and allows it to remain on his body for 24 hours. He then bathes and changes all his clothes. In many cases one

use is that it is sometimes irritating and produces dermatitis

The latest and what appears to be the best drug for the treatment of scabies is the gamma isomer of hexachlorocyclohexane in a vanishing cream base marketed under the trade name of Kwell Ointment. It is white in color and has a faint not unpleasant odor. According to a recent report by Cannon and McRae 100 cases were treated with this new ointment with 100 per cent cures. The remedy was effective in cases in which other preparations had failed. No cases of irritation occurred either as primary or late manifestation and no contraindications were elicited even in the presence of severe secondary dermatitis. The treatment consists of rubbing into the entire cutaneous surface without preliminary bathing a thin film of cream. The patient is requested to refrain from bathing or washing the hands for 24 hours.

He is directed to wear clean underwear and night clothes after the bath and to change the bed linen seeing that all are well laundered before re use. The patient is then re examined at the end of the week.

EDWARD A. OLIVER

ERYTHEMA MULTIFORME

Erythema multiforme requires little treatment except to relieve the symptoms of burning and itching. A soothing lotion of

Zinc oxide	12
Talcum	8
Glycerin	6
Phenol	2
Liquor calcei	120
Aqua roseæ ad	240

dabbed on the affected areas will relieve the burning sensations which often accompany the outbreak of the eruption. If joint pains are present sodium salicylate 10 grains (0.6 gm.) should be given to relieve them every 3 or 4 hours. The bowels should be kept well open and if the patient is running a temperature he should be confined to bed.

The treatment should be directed mainly toward the prevention of a recurrence for these are common in multiforme erythema. A careful examination of the teeth should be made and if abscessed teeth are found

they should be extracted. Tonsillar tissue that is diseased should likewise be removed. Careful inquiry should be made as to the patient's eating habits because the disease is at times a manifestation of a food allergy. Then too the ingestion of some drugs may be an etiologic factor.

When the buccal mucosa is affected and the lips tongue and buccal mucosæ are the seat of painful eroded bullæ soothing antiseptic mouth washes are of value. One of the most useful of these is an iodized phenol mouth wash of

Iodine	2
Phenol	4
Glycerin	6
Alcohol	8
Aqua ad	30

Fifteen drops are diluted in a wineglass of water and used several times a day as a mouth wash.

EDWARD A. OLIVER

DERMATITIS HERPETIFORMIS

Dermatitis herpetiformis is a disease characterized by the development of papules, vesicles and bullæ occurring symmetrically in various sized patches on the limbs, sacral region, the subscapular areas, the antecubital fossæ, the popliteal spaces and on the legs and arms. The eruption is accompanied by severe itching and burning sensations and the disease has the habit of recurring even after all symptoms except the pigmentation left in the wake of the eruption have disappeared.

For that reason the treatment must be continuous. The preparation of most value in the past has been arsenic. This has been given either as liquor potassii arsenitis.

Fowler's solution or in the shape of the Asiatic pill which contains arsenous acid and black pepper. When Fowler's solution is given dosage begins with 3 minims in water three times a day after meals and is increased 1 drop at each dose until the patient is taking 8 drops t.i.d. This is continued until the eruption has involuted then the dose is decreased until a maintenance dose is found. The Asiatic pill is of three sizes $\frac{1}{2}$, $\frac{1}{4}$ and $\frac{1}{8}$ gram. The average patient takes $\frac{1}{8}$ grain four times daily until the symptoms have

disappeared, then continues on a maintenance dose of 1 or 2 pills a day

The objection to the use of arsenic is that the long continued ingestion of this drug produces arsenical keratoses, which later may become carcinomatous. For that reason, the introduction of sulfapyridine in the therapy of dermatitis herpetiformis met with the universal approval of all dermatologists.

Sulfapyridine is now the drug found most valuable for the treatment of this annoying disease. It is given in 1 gm dosage four times a day, with plenty of water and with sodium bicarbonate, for a week or so until the symptoms have lessened, then the dose is cut down to a maintenance dosage of 1.5 gm a day. While the patient is taking sulfapyridine the blood must be carefully examined at frequent intervals and the patient kept under careful observation, because

phenol are of value in controlling the pruritus such as the following

Liquor carbonis detergens	6
Zinc oxide	12
Talcum	8
Glycerin	■
Phenol	2
Alcohol	40
Liquor calcis ad	240

An ointment that I have found of value in relieving pruritus is

Sulfur precip	4
Zinc oxide	8
Amyl	16
Oil of cade	8
Menthol	0.33
Acid salicylic	0.33
Ung petrolatum ad	60

The disease is a serious one and the prognosis is not always good. Persistence for years, with periods of aggravation and decline, is the rule, though some cases do recover completely.

EDWARD A. OLIVER

SEBORRHEIC DERMATITIS

Seborrheic dermatitis is an inflammatory dermatosis, in many cases the result of a superimposed infection upon a pre-existing

seborrhea. It may occur as a scaly, erythematous type of eruption in those areas where the sebaceous glands are most active, i.e., the scalp, eyebrows, chest, and pubic region and it may be a moist fissured type which involves the joint flexural surfaces. The eruption is characterized by a moderate amount of inflammation, yellowish, greasy scales, and occasional crust formations.

Treatment should be directed first to the scalp, regardless of the amount of involvement. A valuable lotion is one containing

Euresol pro capillis	■
Hydrarg bichloride	0.18
Spts formicari	30
Spts odorata	30
Spts vini rectif	70
Aqua dest ad	240

This should be thoroughly rubbed into the scalp once a day, using either the tips of the fingers, after carefully parting the hair or a soft cotton pledget, used instead of the tips of the fingers. This lotion should be used until all symptoms referable to the scalp have disappeared.

If an ointment is preferred, an excellent one is

Sulfur precip	6
Acid salicylic	0.66
Greaseless base ad	60

Numerous greaseless ointment bases are now on the market, and these are much to be preferred to vaseline, lard, or lanolin.

An excellent shampoo to be used once a week is resorcin, 10 per cent or euresol 10 per cent in Ph isoderm.

If there is weeping and crust formation behind the ears wet compresses of dilute aluminum subacetate solution should be used, followed by a 3 per cent vioform cream.

If the retro auricular areas are merely the seat of a scaling fissuring dermatitis, either 3 per cent vioform cream, 3 per cent ammoniated mercury ointment, or an ointment of sulfur precip, 3 per cent and 1 per cent salicylic acid may be used with excellent results. For children with moist, exudative areas in the retro auricular regions painting these areas for 2 or 3 days with a 2 per cent aqueous solution of gentian violet is helpful.

For seborrheic dermatitis, involving the

nasolabial folds chin and eyebrows a 2 per cent sulfur or ammoniated mercury ointment should be used and for patches elsewhere on the glabrous skin 5 per cent sulfur and 1 per cent salicylic acid in a greaseless base will be found valuable

Sulfur in a paste of 40 per cent strength such as

Sulfur precip	12
Vaseline ad	30

is not nearly so irritating as some of the other weaker sulfur preparations and may often be used advantageously behind the ears on the chest and on the face Before using this however a small area should be tested to see that the skin is not allergic to the ointment

For those areas of weeping flexural seborrheic dermatitis encountered in the axillae cubital fossae groins and popliteal spaces excellent results may be obtained with wet compresses of diluted aluminum subacetate solution or 0.25 per cent silver nitrate solution followed by a 3 per cent vioform cream when the parts are dry 3 per cent ammoniated mercury in zinc oxide ointment may be used

Painting moist eczematous areas with a 2 per cent aqueous solution of gentian violet

discolor and stain underwear and bedclothes

General treatment in all cases should consist of the use of fairly large doses of vitamin B complex and intramuscular injections of crude liver extracts

EDWARD A. OLIVER

PSORIASIS

Despite a great deal of investigation little more is known about the etiology of psoriasis than was known 40 years ago The disease may affect the very young or the very old generally it attacks young adults In many cases the lesions will disappear with proper treatment but some cases are most resistant to treatment and the disease invariably tends to recur

The influence of diet is negligible Schamberg found a low protein diet to be of value in some cases I have found that placing

large robust individuals on a low fat or fat free diet is sometimes beneficial

In acute cases where the eruption is wide spread and superficial internal medication is indicated In this type of case Crocker recommended salicin or sodium salicylate Salicin is given well diluted in water in a dosage of 1 gm three times a day Sodium salicylate is given intravenously twice a week in a dosage of 1 gm

Lecithin in the form of acletin capsules (American Lecithin Co) I have also found of value in acute cases These capsules are given in a dosage of 2 capsules three times daily

Madden employs a fat free diet in most cases and uses vitamin B₁ in a dosage of 1000 units a day many dermatologists give injections of the patient's own blood 10 cc being withdrawn from the median basilic vein and re injected into the buttocks immediately every other day for a course of 10 to 12 injections

Arsenic should never be used in acute cases and in chronic resistant cases only for a few months at a time It is best administered as Asiatic pills in a dose of $\frac{1}{10}$ grain (4 mg.) four times a day

Topical Treatment In acute rapidly spreading cases local applications should be soothing Calamine liniment bismuth cream (containing bismuth subnitrate—4 zinc oxide—8 liquor calcis—120 and olive oil ad 240) as well as vioform cream (Ciba) 3 per cent are valuable preparations in this type of the disease

As the disease becomes quiescent we commonly use an ointment of ammoniated mercury 3 per cent and 2 per cent salicylic acid in a greaseless base

If the eruption is localized chronic and in patches an excellent ointment is anthralin ointment This should be used in 0.1 per cent strength to begin with and as tolerance is increased its strength can be raised to 0.25 per cent or even 0.5 per cent

Chrysarobin an old favorite may also be used on chronic patches in 3 to 5 per cent strength with 2 to 3 per cent salicylic acid It may be used as an ointment or incorporated in a paint of traumaticin which is a collodion like mixture

Anthralin and chrysarobin ointments are applied to affected areas once a day and

disappeared, then continues on a maintenance dose of 1 or 2 pills a day

The objection to the use of arsenic is that the long continued ingestion of this drug produces arsenical keratoses, which later may become carcinomatous. For that reason, the introduction of sulfapyridine in the therapy of dermatitis herpetiformis met with the universal approval of all dermatologists.

Sulfapyridine is now the drug found most valuable for the treatment of this annoying disease. It is given in 1 gm dosage four times a day, with plenty of water and with sodium bicarbonate, for a week or so until the symptoms have lessened, then the dose is cut down.

gm a day
pyridine then
administered at frequent intervals and the patient kept under careful observation because sulfapyridine is not a harmless drug and fatalities have followed its usage.

Stimulating lotions containing tar and phenol are of value in controlling the pruritus, such as the following:

Liquor carbonis detergens	6
Zinc oxide	12
Talcum	8
Glycerin	6
Phenol	2
Alcohol	40
Liquor calcis ad	240

An ointment that I have found of value in relieving pruritus is:

Sulfur precip	4
Zinc oxide	8
Amyl	16
Oil of cade	8
Menthol	0.33
Acid salicylic	0.33
Ung petrolatum ad	60

The disease is a serious one and the prognosis is not always good. Persistence for years, with periods of aggravation and decline, is the rule, though some cases do recover completely.

EDWARD A. OLIVER

SEBORRHEIC DERMATITIS

Seborrheic dermatitis is an inflammatory dermatosis, in many cases the result of a superimposed infection upon a pre-existing

seborrhea. It may occur as a scaly, erythematous type of eruption in those areas where the sebaceous glands are most active, i.e., the scalp, eyebrows, chest, and pubic region and it may be a moist, fissured type which involves the joint flexural surfaces. The eruption is characterized by a moderate amount of inflammation, yellowish greasy scales, and occasional crust formations.

Treatment should be directed first to the scalp, regardless of the amount of involvement. A valuable lotion is one containing:

Euresol pro capillis	6
Hydrarg bichloride	0.18
Spts formicari	30
Spts odorata	30
Spts vini rectif	70
Aqua dest ad	240

This should be thoroughly rubbed into the scalp once a day, using either the tips of the fingers, after carefully parting the hair, or a soft cotton pledget used instead of the tips of the fingers. This lotion should be used until all symptoms referable to the scalp have disappeared.

If an ointment is preferred, an excellent one is:

Sulfur precip	6
Acid salicylic	0.66
Greaseless base ad	60

Numerous greaseless ointment bases are now on the market, and these are much to be preferred to vaseline, lard, or lanolin.

An excellent shampoo to be used once a week is resorcin 10 per cent or euresol, 10 per cent in Ph isoderm.

If there is weeping and crust formation behind the ears, wet compresses of dilute aluminum subacetate solution should be used, followed by a 3 per cent vioform cream.

If the retro auricular areas are merely the seat of a scaling fissuring dermatitis, either 3 per cent vioform cream, 3 per cent ammoniated mercury ointment, or an ointment of sulfur precip, 3 per cent and 2 per cent salicylic acid may be used with excellent results. For children with moist, exudative areas in the retro auricular regions painting these areas for 2 or 3 days with a 2 per cent aqueous solution of gentian violet is helpful.

For seborrheic dermatitis, involving the

nasolabial folds, chin and eyebrows, a 2 per cent sulfur or ammoniated mercury ointment should be used, and for patches elsewhere on the glabrous skin, 5 per cent sulfur and 1 per cent salicylic acid in a greaseless base, will be found valuable.

Sulfur in a paste of 40 per cent strength, which

Sulfur precip	12
Vaseline ad	30

is not nearly so irritating as some of the other weaker sulfur preparations and may often be used advantageously behind the ears, on the chest, and on the face. Before using this, however, a small area should be tested to see that the skin is not allergic to the ointment.

For those areas of weeping flexural seborrheic dermatitis encountered in the axillae, cubital fossae, groins, and popliteal spaces excellent results may be obtained with wet compresses of diluted aluminum subacetate solution or 0.25 per cent silver nitrate solution followed by a 3 per cent vioform cream when the parts are dry. 3 per cent ammoniated mercury in zinc oxide ointment may be used.

Painting moist eczematous areas with a

object to the use of these paints because they discolor and stain underwear and bedclothes.

General treatment in all cases should consist of the use of fairly large doses of vitamin B complex and intramuscular injections of crude liver extracts.

EDWARD A. OLIVER

PSORIASIS

Despite a great deal of investigation, little more is known about the etiology of psoriasis than was known 40 years ago. The disease may affect the very young or the very old; generally it attacks young adults. In many cases the lesions will disappear with proper treatment, but some cases are most resistant to treatment and the disease invariably tends to recur.

The influence of diet is negligible. Schamberg found a low protein diet to be of value in some cases. I have found that placing

large, robust individuals on a low fat or fat free diet is sometimes beneficial.

In acute cases where the eruption is widespread and superficial, internal medication is indicated. In this type of case Crocker recommended salicin or sodium salicylate. Salicin is given well diluted in water, in a dosage of 1 gm three times a day. Sodium salicylate is given intravenously twice a week in a dosage of 1 gm.

Lecithin in the form of acletin capsules (American Lecithin Co.) I have also found of value in acute cases. These capsules are given in a dosage of 11 capsules three times daily.

Madden employs a fat free diet in most cases, and uses vitamin B₁ in a dosage of 1000 units a day; many dermatologists give injections of the patient's own blood, 10 cc being withdrawn from the median basilic vein and reinserted into the buttocks immediately every other day for a course of 10 to 12 injections.

Arsenic should never be used in acute cases and in chronic resistant cases only for a few months at a time. It is best administered as Asiatic pills in a dose of $\frac{1}{16}$ grain (4 mg) four times a day.

Topical Treatment. In acute, rapidly spreading cases local applications should be soothing. Calamine liniment, bismuth cream (containing bismuth subnitrate—4, zinc oxide—8, liquor calcis—120 and olive oil ad 240) as well as vioform cream (Ciba) 3 per cent are valuable preparations in this type of the disease.

As the disease becomes quiescent, we commonly use an ointment of ammoniated mercury 3 per cent and 2 per cent salicylic acid, in a greaseless base.

If the eruption is localized, chronic and in patches, an excellent ointment is anthralin ointment. This should be used in 0.1 per cent strength to begin with, and as tolerance is increased its strength can be raised to 0.25 per cent or even 0.5 per cent.

Chrysarobin, an old favorite, may also be used on chronic patches in 3 to 5 per cent strength with 2 to 3 per cent salicylic acid. It may be used as an ointment or incorporated in a paint of traumaticin which is a colloidion like mixture.

Anthralin and chrysarobin ointments are applied to affected areas once a day, and

thoroughly rubbed in. After a week or 10 days of this treatment, a zone of erythema appears about the affected patch and the involved area seems irritated. Treatment should then be stopped and a soothing cream applied until the irritation has subsided when it may be commenced again. Chrysarobin and anthralin should never be used on the face or the scalp and inasmuch as they are both irritating to the eyes the hands should be carefully washed after using them.

For generalized cases either subacute or chronic, the Goeckerman treatment with crude coal tar ointment and ultraviolet light is of great value. This is practical only in hospitalized patients, it is dirty, but efficient. The treatment consists in having the patient anoint himself every night with a crude coal tar ointment of

Crude coal tar	16
Zinc oxide	16
Amyli	120
Petrolatum ad	240

In the morning this is thoroughly removed with olive oil and a good scrub bath with soap and water and the patient then given a generalized lamp treatment, sufficient to produce an erythema. These lamp treatments are given three times a week until the eruption has disappeared.

Crude coal tar ointment is of value in the topical treatment of psoriasis but in cases where the patient objects to ointments that stain one containing 3 to 6 per cent ammoniated mercury and 2 to 3 per cent salicylic acid is valuable.

Psoriasis of the scalp responds best to a greaseless ointment containing 10 per cent ammoniated mercury and 3 per cent salicylic acid. Shampooing twice weekly with 10 per cent euresol or resorcin in Phisoderm is also beneficial. Ultraviolet lamp treatments to the scalp are also of value in cases that resist ointment therapy.

Röntgen therapy in competent hands is a clean efficient method of clearing up chronic cases that fail to respond to ointments. The dose should be 75 r of unfiltered radiation given once a week. Treatments should not exceed six or eight. It must be remembered that psoriatic skin is easily irritated by roentgen rays and overdosage or too many

treatments over a long period of time may lead to radiodermatitis and carcinoma.

Ultraviolet lamp therapy, even without the use of coal tar, is often of value in both acute and chronic cases, but treatment should be strong enough to produce an erythema. Sun baths are also helpful. During the winter months many patients may get relief by basking in the sun in Florida and Arizona. The disease is a stubborn one to treat and recurrences are common. Much can be accomplished, however, by regulating the patient's mode of life and by the judicious use of ointments.

EDWARD A. OLIVER

PITYRIASIS ROSEA

It is often said that pityriasis rosea is a self limited disease for which no treatment is indicated. While in some cases it may disappear with little or no treatment, others may last as long as 6 months. Disfigurement from the eruption and pruritus may be quite marked.

The course of the disease can be shortened and the pruritus helped by producing mild desquamation of the skin by use of the ultraviolet lamp. Three treatments given at intervals of 3 to 5 days, will produce a mild desquamation and generally cure the disease in 2 weeks. For the relief of pruritus the following cream is recommended:

Bismuth subnitrate	4
Zinc oxide	8
Phenol	2
Liquor calcis	120
Olive oil ad	240

Sulfur, tar, and chrysarobin ointments are not indicated in the treatment of this disease. They often will produce a severe dermatitis venenata and prolong the patient's disability.

EDWARD A. OLIVER

LICHEN PLANUS

The cause of this disease is obscure. Numerous clinical observations have confirmed the fact that it frequently occurs in persons who are under nervous strain. Many patients are robust, healthy appearing individuals who work and live under tension. These

patients should be advised to relax to take life easier get plenty of sleep and to take longer and more frequent vacations Some subjects of the disease are neurotic depressed and in poor health These patients will often be helped by a change of climate and environment

Three drugs mercury, bismuth and arsenic are used in the treatment of lichen planus Mercury is the best It may be given by mouth in the form of the protoiodide of

method A 1 per cent solution of bichloride of mercury dissolved in normal salt solution is used and the drug is given in 15 minim dosage deep into the gluteal muscles twice or three times a week This is effective but painful and some patients object to it A preparation less painful is mercury salicylate in oil This may be given in 1 grain dosage twice a week.

Another excellent and valuable preparation, which was off the market during the war is mercuric salicyl arsenate called "Ene-sol" This is not painful and is given in 2 cc dosage intramuscularly twice a week

Bismuth subsalicylate in 2 cc dosage given intramuscularly once a week is not quite so effective as mercury but for patients who do not tolerate injections of mercury it is a valuable substitute It requires from 12 to 15 injections of the bichloride of mercury to clear up the average case of lichen planus and from 8 to 10 injections of bismuth to effect the same result Some cases respond readily to treatment, others are more refractory

Along with intramuscular injections roentgen therapy in competent hands relieves itching and shortens the course of the disease The dosage should be 75 r of unfiltered radiation and this amount may be given to various areas at weekly intervals for five to six treatments with great benefit

For the relief of pruritus until treatment becomes effective the following lotion may be applied to the pruritic areas as often as is necessary

Liquor carbonis detergens	6
Zinc oxide	12
Talcum	8

Glycerin	6
Phenol	2
Magma bentonite ad	240

For the hypertrophic patches that often occur every 2 or 3 weeks is of value

If the disease becomes chronic and there are residues which fail to respond to ordinary treatment arsenic is often beneficial It is best given as the Asiatic pill in $\frac{1}{16}$ grain (4 mg) dosage t i d p c

Lichen planus of the mucous membranes is difficult to cure In many instances patches of lichen planus on the buccal mucosa or on the tongue will remain long after the cutaneous manifestations have disappeared Vitamin B complex either by mouth or by injection has been recommended by Burgess of Montreal who reported success in treatment of this condition in a limited number of cases I have found this form of the disease difficult to cure

EDWARD A. OLIVER

ECZEMATOID DERMATITIS

Atopic Eczema This type of eczema occurs in the infant in the child the adolescent and in the adult It is intimately associated with the atopic forms of sensitivity and there is a close association between this form of eczema and asthma hay fever and migraine In many cases of infantile and childhood eczema a clear cut family history of one of these diseases is obtainable on careful questioning of the parents

INFANTILE ECZEMA The baby's diet should be carefully investigated Many of these children are bottlefed on cows milk Substituting goats milk soybean preparations boiled milk or evaporated milk for cows milk will often prove of value Orange juice and cod liver oil should also be avoided for several months

Soap should never be used on the eczematous skin In its place one may use one of the many detergents now on the market or olive oil Colloid baths however containing soda and starch may be tried The child should be kept in a cool room and the clothing should be light soft and cool Con

tact with wool, silk, and rayon should be avoided and only cotton garments worn

House dust and the substances emanating from mattresses, pillows, bedding, and rugs are often allergenic factors, so they should be avoided as much as possible

The child should be prevented from mutilating his skin by the wearing of cardboard splints in the bend of his elbows, by pinning down the arms of his night clothes to the bedding at night, and by having him wear a soft muslin mask

For topical therapy some form of coal tar affords more relief than anything else. Coal tar should not be used if the child is exposed to strong wind or sunlight shortly after its use because coal tar renders the skin quite photosensitive

Crude coal tar ointment containing

Crude coal tar	2
Zinc oxide	2
Amyl	15
Vaseline	15

may be used in full strength, or it may be diluted with equal parts of vaseline or zinc oxide ointment

Davalan pediatric ointment (Dow Chemical Co.) is an excellent tar ointment. If the baby's skin does not tolerate tar well, an ointment of

Naphthalan	3
Ichthyol	0.66
Zinc oxide	8
Amyl	7
Vaseline ad	30

may be used in its place. Ammoniated mercury ointment is often irritating to the eczematous skin and should not be used

Atopic Eczema in Older Children and Young Adults. Treatment includes three different approaches

LOCAL TREATMENT Pruritus must be alleviated or the patients will scratch and mutilate their skin. Topical remedies, such as crude coal tar ointment, ointments containing phenol in 0.5 per cent or 1 per cent, menthol 0.25 per cent to 0.5 per cent, liquor carbonis detergens and aluminum subacetate solution may be used

Two new antihistamine ointments that will often relieve pruritus and help the eczema are theophorin ointment (Hoff

mann LaRoche, and pyribenzamine cream (Ciba)

Soapless detergents, of which there are many on the market, should be used instead of soap. Soap is not tolerated well by the eczematous skin

ELIMINATION TREATMENT All offending irritants should be eliminated as far as possible. These are dust, wool, silk, rayon, cat hair, and feathers. A simple diet should be prescribed, and foods such as eggs, fish, pork, nuts, cheese, tomatoes, and chocolate should be avoided

If foci of infection such as diseased tonsils or abscessed teeth are present, they should be removed

SEDATION Sedative drugs, such as small doses of phenobarbital, are often indicated in atopic eczema, as these patients are nervous, overactive individuals. The antihistamine drugs, pyribenzamine, hydryllin, benadryl and theophorin should all be tried. In some cases I have found them helpful, in others disappointing

The physician attending these unfortunate individuals should make every effort to understand them. Many of them have problems which they hesitate to talk about. Clearing up these problems may help the disease because here, as in no other disease, is there a psychosomatic background. Many of these patients need psychiatric care, and in many cases a complete change of scene and life in another climate are of more benefit than anything else

Nummular Eczema Nummular eczema occurs in coin sized patches and affects primarily the dorsal surfaces of the hands and forearms and the extensor aspect of the legs and thighs. It is always worse in winter and generally clears in the summer, but has a tendency to recur frequently. Exposure to soap and water, acids and alkalis, as well as oils and grease, favors its development

It is commonly seen in housewives, dish washers, and surgeons, and the foci of infection in the teeth, tonsils, and prostate may be predisposing factors in its development

The disease is a stubborn one to treat. If the patient is anemic and physically below par, suitable tonics should be prescribed. Foci of infection should be removed and since many cases improve in the summer, the patient may be helped by generalized ex-

posures to ultraviolet light and with liberal sized doses of vitamins A and D. A change of climate is also beneficial to some. Mild antiparasitic treatment seems to help this type of eczema more than antieczematous treatment. Painting the lesions with 5 per cent crude coal tar in chloroform is of value.

Vioform ointment 3 per cent (Cib) is also helpful, and painting individual patches with a 3 to 5 per cent solution of silver nitrate every 3 or 4 days, is useful.

When the lesions are dry, the use of crude coal tar ointment is of definite value.

Eczematous Contact Dermatitis. Eczematous contact dermatitis, or dermatitis venenata, is an inflammation of the skin due to occasional, continuous or intermittent contact with a cutaneous irritant. Among the common causes of contact dermatitis are

(1) *Plants*, such as primroses, chrysanthemums, the Rhus family of ivy, oak and sumac, ragweed, geranium, and tomato plants.

(2) *Drugs*: Alkalies, soaps, soda, butyn, cocaine, novocain, iodoform, picric acid, and resorcin.

(3) *Miscellaneous Irritants*: Hair dyes, clothing dyes, depilatories, nail polishes, cosmetics, adhesive plaster, and dress shields.

The dermatitis may be acute or chronic. If acute it is characterized by redness, edema and the formation of papules and vesicles. If chronic it is characterized by scales, crusts and infiltration of the skin.

The first essential of treatment is to remove the cause, if this can be discovered. Careful history taking will often give a definite clue as to what has produced the dermatitis.

When the involved parts are acutely inflamed, wet dressings are indicated. One of the best preparations to use on an inflamed skin is aluminum subacetate solution, diluted 1 oz. to 1 pint of cool water or cool milk and applied in the form of wet compresses.

Dilute solutions of subacetate of lead are also of value, and if infection is superimposed on an inflamed skin wet dressings of silver nitrate, aqueous solutions of boric acid of 1 to 4 strength are beneficial. Compresses of a 1:4000 solution of potassium permanganate are also of value in pustular dermatitis.

As the inflammation subsides lotions or ointments may be used. The familiar calamine lotion or the following lotion may be used with benefit:

Zinc oxide	12
Talcum	8
Glycerin	II
Phenol	2
Liquor calcis	120
Magma bentonite ad	240

When the parts are dry, the following ointments will prove helpful in curing the dermatitis:

(1) Ichthyol	66
Calamine	4
Zinc oxide	4
Ung. aqua rosae ad	30
(2) Naphthalan	3
Ichthyol	0.66
Zinc oxide	8
Amyli	7
Vaseline ad	30
(3) Crude coal tar	2
Zinc oxide	2
Amyli	15
Vaseline ad	30
and Lassar's paste	

EDWARD A. OLIVER

TINEA VERSICOLOR

This is a common superficial fungous infection and is often present for months before the patient seeks treatment. The disease is marked by fawn colored patches of various sizes, most often seen on the chest and anterior trunk.

The treatment is simple. The patient is instructed to scrub the affected parts at night with soap and water. While the skin is still moist, a solution of vinegar is dabbed on the affected areas, and while this is still

per
tion
with
the sodium hyposulfite solution produces nascent sulfurous acid which rapidly kills the fungus and cures the disease in a week to 10 days.

A half strength Whitfield's ointment, such as

Acid salicylic	1
Acid benzoic	2
Ung petrolatum	15
Ung aqua rosae	15

will also clear up the condition rapidly if applied to the affected areas for about a week

EDWARD A. OLIVER

PRURITUS ANI

This somewhat common condition is often seen in high strung, nervous, and tense individuals. It may, however, occur in normal, well balanced, and even phlegmatic persons.

There are many causes besides nervous tension. Fungous infection may be present, the patient may be allergic to toilet paper or toilet soap, he may have a pinworm infection of the bowel or he may suffer from hemorrhoids, fissures, and polyps. Liver disease also may be a factor in the production of anal pruritus.

In every case a complete history should be taken and a careful examination made. If the patient has a fungous infection (tinea cruris) in the groin or between the toes, that infection should receive treatment. Hemorrhoids, fissures, and polyps should be excised.

Many patients respond to simple combined treatment, which includes the use of roentgen rays, topical remedies, sedation and diet.

The diet should be bland. Spices, alcohol, and foods containing small seeds should be avoided. Coffee should be limited to 1 or 2 cups daily, and the use of tobacco should be curtailed.

The patient should never use soap on the affected parts. The too energetic use of soap in taking a shower bath often starts pruritus ani. Considerable relief may be had by taking a hot sitz bath, medicated or unmedicated. For these sitz baths camomile tea and potassium permanganate are among the better antipruritic agents. If camomile tea is used, an infusion should be brewed and from 10 to 25 cc used in a tub of water. In using potassium permanganate, dissolve 1

teaspoonful or 1 tablespoonful of crystals in a quart of water, and use 1 quart to a tub of water. Care should be taken to see that the crystals are completely dissolved. Otherwise contact with the skin produces a burn.

The patient should cleanse the parts immediately after defecation with a warm wet wash cloth or with moist absorbent cotton. Toilet paper should not be used. It is also a good procedure to have the patient apply zinc oxide ointment to the anal area before defecation, removing it immediately after ward with olive oil, and then using the prescribed medication.

For topical remedies some patients prefer lotions, others prefer ointments. If lotions are used, I often prescribe the following one: keeping a pledget of cotton saturated with it in the anal crease for a week or so until the patient gets relief.

Zinc oxide	12
Talcum	8
Glycerin	6
Phenol	2
Liquor calcis	120
Magma bentonite q s ad	240

To this may be added liquor carbonis detergens 6 to 12 gm.

If the parts are moist and macerated, a monilia infection may be present, then painting with a 2 per cent solution of gentian violet or a 0.5 to 1 per cent solution of brilliant green will be effective.

If there is considerable inflammation and eczematous reaction present, wet compresses of aluminum subacetate solution, diluted 1 ounce to 1 pint of cool water, or silver nitrate solution diluted 2 teaspoonfuls of a 10 per cent solution to 1 pint of cool water, are indicated.

If a fungous infection is present, either of the following ointments or the lotion, will prove effective.

Sulfur precip	1
Acid salicylic	1
Cold cream	15
Vaseline	15
or	
Acid salicylic	0.66
Acid benzoic	1.2
Cold cream	15
Vaseline	15

	or	
Resorcin		12
Calamine lotion	ad	240

In uncomplicated cases good results will often be obtained with mercury. A good ointment to use is

Hydrarg ammoniatum	1
Ung zinc oxide ad	30
or	
Pulv calomel	4
Boric acid	4
Menthol	0.15
Cold cream ad	30

The new antihistamine ointments, theophorin ointment (Hoffmann-LaRoche) or pyribenzamine cream (Ciba) often give prompt relief.

Coal tar ointments, such as

Davalan ointment	15
Ung zinc oxide	15
	or
Crude coal tar	2
Zinc oxide	2
Amyli	15
Vaseline	15

are also valuable.

The patient may require sedation, and in that case phenobarbital in dosage of $\frac{1}{2}$ to $\frac{1}{4}$ grain (15 to 30 mg) may be given three or four times daily.

The antihistamine drugs, hydriylin, pyri-

benzamine, or benadryl, are often of considerable value in relieving pruritus, as is acid acetylsalicylic in 5 grain (0.3 gm) doses, three or four times daily.

Röntgen therapy is one of the best remedies we have for the control and even cure of this annoying condition. In competent hands, roentgen therapy will do more to give the patient complete relief than almost any other remedy. A dose of 75 r is given to the affected area once a week for from four to six treatments. In most cases this amount will alleviate most of the pruritus, and treatment should be stopped. If there is a recurrence, four more such treatments of 75 r unfiltered may be given. It is not safe to give more than this amount. Radiodermatitis and other unfortunate sequelae may occur.

Finally if all these measures fail injection of alcohol by a competent surgeon may effect a cure.

EDWARD A. OLIVER

REFERENCES

- Andrews G C *Diseases of the Skin a Textbook for Practitioners and Students* Ed 3 Philadelphia W B Saunders Company 1946
 Lewis G M and Hopper M E *An Introduction to Medical Mycology* Chicago The Year Book Publishers 1948

INDEX

Abdominal abscesses 375
Abscess, mediastinal 389 390
 perirectal 344
 pulmonary
 (See Pulmonary abscess)
AC (Bayer 7602) 161
Acacia, 516 517
ACE (adrenocortical extract), 602
Acetarsone, 335
Acetic acid
 crystals 330
 urea verucolor 683
Acetophenetidin, 638
Acetyl beta methylcholine 400, 401
Acetyl methylcholine chloride 396
Acetyl salicylic acid
 (See Aspirin)
Achilles tendon 482
Achilles 231 233 235 253 254 255 340
alkali therapy 255
 bronchitis 254
 cardiac failure 254
 diabetes mellitus 231 233 235 255
 diarrhea 254
 edema pulmonary 254
 emphysema, 254
 gastro 255
 molar sodium lactate solution 255
 molar sodium 254
 oxygen therapy 255
 strabismus, 255
 thrombo-ulcerative colitis chronic 340
 uremia 255
Achalasia 321
Acho 672-674
 comedones 673
 constipation 674
 diet 672 674
 hydrochloric acid dilute 674
 ketosis 674
 leukemia 672
 leukosis 673
 ointments 673 674
 psoriasis 673
 rhinophyma 674
 rosacea therapy 673
 rosacea 673 674
 sulfur 673
 ultraviolet lamp therapy 673
 vitamin B complex 674
 Vitamin K solution 673 674
Actinobacillus 330
Actinobacillus 470
Actinobacillus
 (See Scleroderma)
Actinobacillus
 (See Scleroderma)
ACTH (adrenocorticotrophic hormone)
 adrenocorticotrophic 590
 alarm reaction 589 590
 alcoholism acute 602
 anaphylactic reactions 590
 anxiety nervous 309
 asthma rheumatoid 533, 541 542 590
 asthma bronchial 533
 colitis thrombo-ulcerative 339
 ulcerative 590
 Cushing's syndrome 590
 dissecting lupus erythematosus 197
 dosage, 590
 fruit 531 553 554 590
 hyperglycemia 590
 hypertension essential 590
 infectious diseases acute 590
 myasthenia gravis 590
 nephrosclerosis 590
 nephrotic syndrome 518
 dermatitis nodosa 458
 rheumatic fever 49 590
 scleroderma 472
 Actinomyces 130 132 390 548
 abscess 148
 bed rest 131
 blood dyscrasia 131
 copper sulfate 130 132
 ethyl iodide inhalant on 131
 ferrous sulfate 131

gentian violet 132
hematuria 131
iodides 131 132
lobectomy 131
Lugol's solution 132
mediastinal abscess 390
penicillin 130, 131 132
potassium iodide 130 131
radium 130
roentgen therapy 130 131
skin eruption 131
sodium iodide 130 131
streptomycin 132
sulfadiazine 130 131
surgery 130 131
systemic type 130 131
thymol 130 132
vacuum 130 132
vitamins 131
Acute arterial thrombosis
 (See Sudden arterial occlusion)
Acute bacterial endocarditis 479-480
 aureomycin 479
 chloromycetin 479
 penicillin 479
 Pneumococci 430
 Staphylococcus aureus 430
 Streptococcus Anomalous 430
 streptomycin 479
Acute diffuse necrosis of the liver
 (See Acute yellow atrophy of the liver)
Acute gastro-enteritis
 (See Gastro-enteritis)
Acute infectious hepatitis
 (See Hepatitis)
Acute melioidosis 108 109
Acute myocarditis of infectious disease 431
Acute poliomyelitis
 (See Poliomyelitis)
Acute serum hepatitis
 (See Hepatitis)
Acute yellow atrophy of the liver 351
 352
 anemia 352
 barbiturates 352
 calomel 352
 coma hepatic 352
 ergotamine tartrate 352
 glucose 351
 lactic acid 352
 methionine intravenous 351
 oxygen administration 351
 plasma, stored 351
 procaine hydrochloride intravenous 352
 protein intravenous 351
 pruritus 352
 transfusions of whole blood 352
 vitamin K, 351 352
Addison's disease, 245 256 260 446 589
 acute adrenal insufficiency, 258 259
 adrenal cortical extract 257 259 260
 anion acid 256
 antibiotics 259
 cardiac decompensation 446
 compounds A, E, F 589
 cortisone 258
 desoxy-cortisone acetate 256 257
 258 259, 260
 intramuscular injection 257
 intra-oral administration 258
 pellets 257 258
 sublingual administration 258
 diet 256 257
 epinephrine 259
 glucose, 258 259
 grate of adrenal gland 258
 hypoglycemia functional 245
 infections acute 259
 pregnancy 259 260
 protein hydrolyzates 256
 and vanadium 256 257 259 260
 surgery 259
 testosterone propionate 258
 transfusions 259

Adolescent spondylitis
 (See Arthritis rheumatoid)
Adrenal cortical extract
 Addison's disease 257 259 260
 bromide intoxication 609
 (See also Cortisone)
Adrenalin
 anemia pernicious 479
 bronchiectasis 371 372
 bronchitis chronic 371 372
 diphtheria 371
 emphysema 375
 influenza meningitis 52
 leishmaniasis, 159 160
 pneumonia 45
 purpura, nonthrombocytopenic 509
 serum sickness 586
 (See also Epinephrine)
Adrenocorticotrophic hormone
 (See ACTH)
Aedes aegypti 34
Aerobacter aerogenes
 cholesterol 361
 pyelitis 528
 pyelonephritis 528
 urinary tract infections 202
Aerodentalgia 595
Aero-embolism 394-395
Aerobacillus 595
Aerobacillus
 bronchiectasis 370 372
 bronchitis chronic 370-372
 emphysema 375
 Löffler's therapy 387
 pneumonia 42
 pulmonary abscess 393 394
 pulmonary fibrosis 376
 tracheobronchitis acute 370
African sleeping sickness 161
African tick fever
 (See Relapsing fever)
African trypanosomiasis 161
Agranulocytosis 50 263 264 265 361
 489 590
 ACTH 590
 chloretal, 361
 cortisone 590
 hyperthyroidism 263 264 265
 meningococcal meningitis 50
 A. S. disease 393 394
 Albumin 148 315 317
Alcohol
 alcoholism acute 601
 anaphylaxis 410
 arterial occlusion sudden 467 468
 arteriosclerosis obliterans 463
 asphyxia 140
 cerebral circulatory disturbances 629
 coronary insufficiency 410
 dermatitis herpetiformis lesion for 678
 epilepsy 654
 erythema multiforme mouth wash for, 677
 erythromelalgia injection for 471
 glomerulonephritis chronic 519
 gonorrhea 24
 headache injection for 641
 hepatitis, 38, 39
 hypertension poisoning 603
 myocardial infarction acute 419
 paraplegia as lesion of the spinal cord injection for 664
 pruritus and injection for 655
 Raynaud's disease 469
 sudden arterial occlusion 467 468
 thrombocytopenic purpura 463
Alcoholism acute 600 602
 ACE 602
 ACTH 602
 alcohol administration 601
 amphetamines 600 601
 apomorphine hydrochloride 600
 artificial respiration 601
 barbiturates, 600 601
 carbon dioxide 601
 caramum 601
 delirium tremens 601

- Alcoholism—(continued)**
 desoxyphenazine 601
 dextrose 601
 insulin 601
 methenism 601
 metrazol 601
 paraldehyde 600 601
 picrotin 601
 vitamin B complex 601
- Aldersone 191**
Alimentary tuberculosis 334 336
 acetarsone 335
 antibiotics 335
 arsenic 335
 bed rest 334
 calcium chloride 335
 calcium gluconate 335
 cod liver oil 334
 colocolostomy 335
 compl. cabons 336
 diarrhea 334
 diet 334
 dihydrostreptomycin 335
 heliotherapy 334
 hyperplastic 334
 ileocolostomy 335
 illustrative case 335 336
 mercury 335
 oxygen inject on into peritoneal cavity 334
 parathyroid solution 335
 promin 335
 roentgen therapy 334
 sodium chloride 334
 streptomycin 335
 sulfanilamide 335
 sulfapyridine 335
 surgery 335
 trepanol 335
 ulcerative 334
 vitamins 334
- Alkalemia**
 (See Alkalosis)
 Alkali poisoning 321
 Alkalosis 253 254 255 340
 alkali therapy 254 255
 ammonium chloride 255
 anoxia 254
 cardiac failure 254
 glucose 255
 hyperpnea 254
 hyperventilation 254 255
 hysteria 254
 neuromathema 254
 peptic ulcers 254
 tetany 255
 therapy 255
 thrombo-ulcerative colitis chronic 340
- Allergy diseases due to 567 588**
 nasal due to fungi
 (See Nasal allergy)
Aluminum acetate solution 683 684
Aluminum hydroxide
 hyperchlorhydria 320
 peptic ulcer 317 326 327 331
 preoperative preparation of jaundiced patient 358
Alum. num phosphate 326 331
Alum. num subacetate solution
 eczema atop. 682
 seborrheic dermatitis 679
 tinea glabra 674
 tinea pedis 675
Amberlite 326
Amblyopia 189 194 199 203
 alderson 191
 arsen calis 191
 aureomycin 192 193 194
 bacracura 192
 bed rest 191
 carbazone 191
 chaparro 191
 chinolone 191
 chloraquine d phosphate 193 194
 chloroverin 193
 diet 190 191
 diodquin 191
 electrocardiograms serial 193
 emet. ne 191 192 193 194
 Eckerichia coli 190
 Eckerichia histolytica 190
 Eckerichia magna 190
 podocyanine compounds 191
 penicillin 192
 streptomycin 192
 sulfonamides 193
 terramycin 193 203
 terramycin 191
- Amenorrhea 276-278 309 311, 312**
 anemia 277
 anoxia nervosa 309 311 312
 estrogen 277 278
 pelvic abnormal ties 277
 primary type 277
 progesterone 278
 roentgen therapy 278
 secondary type 278
 sterility 278
 stilbestrol 278
 substitution therapy 277
 thyroid extract 277
 tuberculosis 277
 vaginal examination 277
Amethepteron, 491 492
Amigen
 hepatitis toxic 350
 pancreatitis acute 364
 pertussis 357
 preoperative preparation of jaundiced patient 358
 (See also Amino acids and Protein hydrolysates)
Amino acids
 Addison's disease 256
 anemia 384
 bronchiectasis 374
 bronchitis chronic 374
 etiac syndrome 367
 cholelithiasis acute 360
 cirrhosis of the liver 353
 diabetes mellitus 234
 diptheria 83
 enteritis regional 333
 hepatic insufficiency 356
 hepatitis 38
 hypod nephrosis 375
 myasthenia gravis 364
 nephritis 375
 paraplegia in lesions of spinal cord 662
 pertussis 87
 pneumonia 46
 preoperative preparation of jaundiced patient 358
 urem. a. exsurreal 524
 (See also Amgen and Protein hydrolysates)
Aminoophylline
 angina pectoris 411 412
 asthma, bronchial 578 579
 atelectasis 378
 auricular fibrillation 403
 cardiac decompensation 440 444
 cerebral arteriosclerosis 634
 cerebral circulatory disturbances 632
 coronary insufficiency 411 412
 myophycin 375
 hay fever 570
 heart block 405
 lower nephron nephrosis 526
 myocardial infarction acute 415 418
 422
 paroxysmal ventricular tachycardia 401 402
 pleurisy with effusion 385
 pneumothorax 41 45
 surgical patient with heart disease 436
 uremia gravis 522
Aminopyrine 491 492
Aminopyrine
 agranulocytosis caused by 489
 measles 638
 headache 638
 measles 13
 rheumatic fever 68
 ammonium chloride 560
 ammonium chloride
 alkalosis 255
 cardiac decompensation 440 444
 glomerulonephritis acute 513
 hepatic insufficiency 356
 hyperventilation syndrome 391
 lead poisoning 615
 lower nephron nephrosis 526
 Meniere's syndrome 670
 nephrotic syndrome 517 518
 pericarditis chronic constr. etc 433
 uremia, extrarenal 524
Ammonium citrate
 anem. a. hypochrom. c 483
 glomerulonephritis acute 514 515
 chron. c 520
Ammonium mandelate 527
Ammonium nitrate 518
Amphofyl 275
Amyl nitrate
 angina pectoris 411
 headache 639
- Amyloidosis of thyroid 271**
Amytal sodium
 (See Sodium amytal)
Anaesthesia 346
Anaphylactoid reactions 590
Anayodin 191
Ancylostoma braziliense 214
Ancylostoma duodenale 212 213
Ancylostomiasis 212 214
 alcoholism 213
 anemia 213
 carbon tetrachloride 213
 chenopodium oil of 213
 creeping eruption 213 214
 diet 213
 hexylresorcinol 213
 iron 213
 Löffler's syndrome 214
 magnesium citrate 213
 Necator americanus 212
 prevention 214
 tetrachloroethylene 213
 thymol 213
 vertigo 213
 vitamins 213
- Androgens**
 menopause 282 283
 menorrhag. a 279
 osteoporosis 559
 scleroderma 472
Anem. a. achrest. c 482
 hemolytic c 361 484-485
 acute 485
 cholelithiasis acute 361
 coal tar derivatives caused by 485
 cold agglutinins 485
 congenital type 484
 fava bean caused by 485
 glucose 485
 lead compounds caused by 485
 Lederer's type 484
 malaria 485
 phenylhydrazine caused by 485
 serum agglutinins 484
 sickle cell type 484
 sodium bicarbonate 485
 sodium lactate 485
 splenectomy 484
 splenomegaly 484
 streptococcal infections 485
 streptococcal infect. cns 485
 sulfonamide des. caused by 485
 thalassemia 484
 transfus. cns 484 485
 hypochromic 482 484
 ammonium citrate 483
 cancer 483
 copper 483
 ferrous gluconate 483
 ferrous sulfate 483
 hydrochloric acid 483
 infections 483
 molybdenum 483-484
 sickle cell type 483
 thalassemia 483
 hypoplastic 481-482
 benzene exposure to 481
 benzene 481
 hemorrhage 481 482
 leukopenia 481 482
 penicillin 482
 protein, ne 481
 sulfonamide des. 482
 toluene blue 481
 thrombocytopenia 481 482
 transfusion of whole blood 481
 transfusion of infancy 481
 macrocytic of infancy 481
 of nutritional deficiency 481
 of pregnancy 480
 myelophthisic 482
 pernicious 478-480
 achlorhydria 480
 adrenal n 479
 extral. 478
 folic acid 479 480
 hydrochloric acid dilute 480
 iron therapy 480
 liver extract 478 479 480
 ventr. culin 478
 vitamins 478 479 480
 splenic 485-489
 Bant's syndrome 488
 Gaucher's disease 488
 Hand-Christian-Schüller disease 488
 Letterer-Siwe disease 488
 Nemman Pick disease 488
 primary splenic p. panhematopoietic 489
 roentgen therapy 489
 splenectomy 488 489
 transfusions 489

- Angina decub (us 408 410 411 412
Ang na pectoris
(See Coronary insufficiency)
Ang oedema
(See Urticaria)
Anhidrosis in orthostatic hypotension 457
458
Anorexia nervosa 309 313
ACTH 309
amenorrhea, 309 311 312
anemia 312
anterior pituitary insufficiency 309 310
belladonna tincture of 312
diet 311-312
diethylstilbestrol 312
edema 312
estrogens 312
gonadotropic hormone 309
leukopenia 312
lymphocytes 309 312
osteoporosis 312
phenobarbital 312
psychologic factors 310
pylorospasm 312
renal calculi 310
"rheumatoid disease" 309
stomach roentgenoscopies of 311
thyrotrophic hormone 309
vitamins 311 312
Antibismal ne
Ariarasis 215
granuloma inguinale 162
leishmaniasis 150
schistosomiasis 206 207
Anthrax 381
Anthrax treatment 675 679 680
Anthrax 104 107 199 202
ant anthrax serum 105 106
aureomycin 105
meningitis 106
neocarphenamine 105 106
pneumonia 106
rheumatism 106
streptomycin 105 106
sulfadiazine 105 106
sulfathiazole 105 106
tetracycline 199 202
Antibacterial serum 105 106
Anti-Candida albicans rabbit serum 133
Anti-Candida albicans rabbit serum 339
Anti coagulants
endocarditis subacute bacterial 428
myocardial infarct on acute 419-421
pulmonary embolism 370 340
subacute bacterial endocarditis 428
(See also Dicumariol and Heparin)
Antihistamines
angioneurotic edema 584
asthma 377
bronchitis 371
bronchitis chronic 371
common cold 3
dormant lupus erythematosus 396
397
emphysema 373
erythema nodosum 196
hay fever 570 571
headache 647
herpes zoster 11
laryngitis 369
Löffler's syndrome 387
endocarditis 216
Dermatitis nodosa 458
scleroderma 477
swimmer's itch 207
syphilis 168, 170
tracheobronchitis acute 369
urticaria 384
Anti-influenza rabbit serum 52 54
Antimony
filariasis 215
fluke infections 205
granuloma inguinale 162 163
histoplasmosis 136
leishmaniasis 158 159
multiple myeloma 510
schistosomiasis 206
Antiplague serum 99
Antipneumococcal rabbit serum
bronchopneumonia 88
pneumococcal meningitis 56
pneumonia 44
Antipyretics 35
Antipyrine 638
Antivena 616 617
Antivena 283
Aorta dissecting aneurysm 455-457
Aphthous fever 36
- Aplastic and primary refractory anemia
481 482
Apomorphine hydrochloride
alcoholism acute 600
asthma bronchial 379 380
Apoplexy
(See Cerebral circulatory disturb
ances)
Appendicitis
coronary insufficiency 409
esophagitis 317
pylorospasm 320
Aqueous zephiran chloride 17
Arakia, 153 154
Argyrol 50
Arsenolite 215
Arsenic
allimentary tuberculosis 335
anthrax 191
bronchitis 373
dermatitis herpetiformis 677
epilepsy 655
filariasis 215
leukemia chronic granulocytic 496
lichen planus 681
malaria 154
multiple sclerosis 648
poisoning 321 610 612
acute 610
BAL 610-612
chronic 612
coramine 610
epinephrine 610
ferrous hydroxide 610
gastrol 610
magnesium sulfate 610
metrazol 610
plasma infusion 610
sodium chlorate 612
poisoning 679
pulmonary abscess 383
purpura thrombocytopenic caused by
309
rat bite fever 157
relapsing fever 156
syphilis, 168 169 176
tuberculosis alimentary 335
"venereal" angina 314
"viral" C 299
Arsenic poisoning 612
Arsenic 651
Arterial embolism
(See Sudden arterial occlusion)
Arterial occlusion sudden
(See Sudden arterial occlusion)
Arteriosclerosis obliterans and thrombo
sclerosis obliterans 459-466
alcohol 462 463
amputations 464-465
anesthesia of sympathetic nerves
463
angio 463
barbiturates 463
bed rest 459
bowen acid 464
chiropractic 461
choline chloride 461
codeine 463
demerol hydrochloride 463
diabetes mellitus 461
diathermy 462
diastol 463
dolanine 463
education of patient 460 461
erythrocytes 464
ether intravenous 465
feet care of 460 461
fungus control 461
gangrene 464 465
heat therapy 462
heparin 461
hormone 465
liped 461
mechanical methods for increasing cir
culation 462-463
morphine 463
oscillating bed 462 463
pain control of 463
pancreatic tissue extract 463
pantopon 463
papaverine 462
penicillin 464
polycythemia 461
potassium permanganate 461 464
pruritus 465
salicylates 463
"Sander's oscillating bed" 462 463
secural 463
sodium chloride hypertonic 462
- sulfathiazole ointment 462
surgery 461
sympathomimetic 462
sympathetic nerves anesthetization of
462
temperature warm environmental 459
461
tetra-ethyl-ammonium chloride 462
thyroid 461
tobacco 460
trichophytosis 462
typhoid fever 464
ulceration 464
vaccine typhoid 462
vasodilation 461 462
vitamin E 465
Arteritis temporalis headache 645 646
Arthritis
actinomycosis 548
bacillary dysentery 96
brucellosis 549
coccioid 548
colitis regional ulcerative 344
gonorrheal 74-75 547
meningococcal 548 549
meningococcal meningitis 50
menstrual 295
regional ulcerative colitis 344
rheumatoid 533 543 590
ACTH 515 541 542 590
aspirin 540
BAL 530 540
cervix 537
chrysotherapy 537 540
codonate 540
cortisone 533 541 542
Cushings syndrome 542
demerol 540
diagnosis 533 534
diet 540
eggs 535
fever therapy 536 537
gold therapy 537 540
heat therapy 535
heliotherapy 537
hyperadrenalism 542
infections focus of 537
juvenile 542
massage 535
mochrylone 538
occupational therapy 535 536
orthopedic measures 541
paraffin dips 535
phenobarbital 540
physical therapy 537
prostatic secretions 537
psoriasis 542
psychiatry 536
rehabilitation occupational 536
physical 536
relapses after gold therapy 538
rest 534 535
roentgen therapy 536 543
salicylates 540
sanctuary 538
senses 537
spondylitis 533 542 543
Still's disease 542
teeth care of 537
tonsils 537
toxic reactions to gold therapy 539
typhoid vaccine therapy 538
vitamins 537
scarlet fever 54
staphylococcal infections 548
streptococcal infections 548
tuberculosis 547 548
vitamin D deficiency 302
Arthritis phenomenon in diphtheria 83
Articular infections 546 549
Articular resorption
alcoholism acute 601
carbon monoxide asphyxia 596
electric shock 595 596
Asbestos 38
Ascariasis 209 210
Ascites 210
Ascariasis lambricoides 209
belladonna 210
chenopodium oil of 210
diarrhea 210
hexylresorcinol 210
morphine 210
nausea 210
oil emulsion 210
paraffin oil 210
prevention 210
tetrachloroethylene 210
Ascariasis lambricoides 209

- symptoms 604
 vitamins 608
Bartolella bacilliformis 347
 Bartolella disease, 147
 Bayer 205
 oschercerianus 216
 trypanosomiasis African 161
 Bayer 1601
 trypanosomiasis South American 161
 Be et 153
 Belladonna
 anorexia nervosa 312
 ascariasis 210
 cardiochiasm 318
 colon functional disorders of 345 348
 cystitis 519
 esophagitis 316
 gastritis, chronic hypertrophic 323
 gastro-enteritis 36
 heart block 405
 ileus 391
 myasthenia gravis 563 564
 paracercariasis chronic 345
 parkinsonism 631 632 633
 paroxysmal auricular tachycardia, 401
 peptic ulcer 317 326 328
 pylorospasm, 320
 tachycardia, paroxysmal auricular 401
 (See also Atropine)
 Bell's palsy 668
 Benadryl
 angioneurotic edema 584
 bronchitis chronic 371 372
 bronchitis chronic 371 372
 eczema atopic 583
 emphysema 375
 hay fever, 370
 headache 647
 laryngitis 368
 pruritus ani 683
 rhinitis allergic 373
 serum sickness 587
 urticaria 584
 Bends 594 595
 Benemid 426
 Benzidine
 alcoholism acute 600 601
 barbiturate poisoning 605 607
 epilepsy 658
 headache 630 638 647
 hypotension orthostatic 457
 obesity 247 248
 narcotism 660
 parkinsonism 632, 633
 anemia hypoplastic caused by 481
 leukemia chronic granulocytic 496
 purpura thrombocytopenic caused by 559
 pruritus ani 684
 subacute bacterial endocarditis 426
 tinea glabra 674
 Benzoic acid 675 684
 Benzoin 368 369
 Benzyl benzoate
 bilantidians 195
 scabies 676
 trichomoniasis 145
 Berberine sulfate 160
 Beriberi 292 293
 Beta naphthol, 205
 Bernal 138
 Bichloride of mercury poisoning 612-613
 Bilateral bronchogenic tuberculosis 323
 Bilateral renal tuberculosis 129
 Bitron 362
 Bismuth
 bacillary dysentery 94
 bronchiectasis 373
 diarrhea 90
 dissecting latent lupus erythematosus 196
 gastro-enteritis acute 36
 leaden plagues 681
 malaria 154
 peptic ulcer 317 326
 pityriasis rosea 680
 psoriasis 679
 pulmonary abscess 383
 relapsing fever 156
 salmonellosis 93
 scleroderma 472
 syphilis 168 169 170 171 173 176
 ulcer peptic 317 326
 Black widow spider bite 617 618
 Blackwater fever 154 155
 anuria 155
 barbiturates, 155
 falciparum infections 154
 hemoglobinuria 154
 malaria 154 155
 oliguria, 155
 quinacrine 153
 quinine 154 155
 mortality rate 155
 renal ischemia 155
 sodium chloride 153
 transfusions 153
Blasiotomyces dermatitidis 153 154, 156
Blasiotomyces 153 154
 antiblastomycosis rabbit serum 153
 coccidiosis dermatitis progressive 154
 copper sulfate 153
 diet 152
 ethyl iodide inhalation 155
 glucosin 154
 iodides 152 154
 med. animal abscess 390
 penicillin 153
 potassium iodide 153
 roentgen therapy 153
 sodium iodide 153
 streptomycin 153 154
 sulfonamide 153 154
 surgery 153
 vaccine 152 153
 vitamin 152
 Blindness in methyl alcohol poisoning 602
 Bone marrow extract 439
 Bone acid
 arteriosclerosis obliterans 464
 aspergillosis 140
 chickenpot 16
 cystitis 530
 osteitis 43
 osteomyelitis 157
 pruritus ani 683
 Rickets disease 197
 smallpox 17
 smallpox vaccine on 18
 thrombosis obliterans 464
 tinea pedis 675
 Boric 155
 Boreas 317 318
 Bradycardia 457
 Brill's disease 144
 Brilliant green 675 679 684
 Bromides
 atelectasis 377
 bronchitis chronic 372
 bronchitis chronic 372
 colon functional disorders of 346
 coronary insufficiency with angina pectoris 411
 emphysema, 375
 epilepsy 655 656
 extrastolic, 404
 headache, 639
 intoxication caused by 608 609
 laryngitis, 368
 Löffler's therapy 352
 tachycardia paroxysmal auricular 401
 tracheobronchitis 369
 Bromsulphalein test in hepatic insufficiency, 355
 Bronchial asthma
 (See Asthma bronchial)
 Bronchial destruction in pneumonia 40
 Bronchial tuberculosis 123 124
 Bronchiectasis
 (See Bronchitis chronic)
 Bronchogenic tuberculosis 120 121 123
 Bronchitis chronic and bronchiectasis 203, 370-374 581
 acetyl therapy 370 372 373
 adrenalin inhalation on 371 372
 antiblastomycosis 371
 benadryl hydrochloride 371 372
 bronchoscopic aspiration 375
 iodides 371
 penicillin 370 371 372
 streptomycin 371 372
 sympathomimetic drugs 371
 tyrothricin solution on 371 372
 allergens 371
 amino acids 374
 arsenic 373
 asthma bronchial 581
 barbiturates 372 373
 bismuth 373
 bromides 372
 candida albicans 372
 candida 372 373
 cough, 371 372 373 374
 diet 374
 edema 371 373
 expectorants 373
 morphine, 372
 postural drainage 373
 pneumothorax 373
 roentgen therapy 374
 sulfates 377
 spasm 371 373
 surgery, 374
 terpin hydrate 373
 terramycin 373
 transfusions of whole blood 374
 vaccine 374
 Vaponefrin apparatus 370
 vitamins 374
 Bronchopneumonia
 meningococcal meningitis 50
 pertussis 88
 Bronchopulmonary geotrichosis 143
 Bronchopulmonary moniliasis 139
 Bronchospasm
 atelectasis 378
 polymyositis acute 32
 pulmonary abscess 383
 Bronchiolitis 15 372
Brucella abortus 75
Brucella melitensis 75
Brucella suis 75
 Brucellosis 75 77 198 199 201
 alkali 77
 a. thubus 349
 ascorbic acid 77
 streptomycin 77
 bed rest 77
 dihydrostreptomycin 76
 glucose 77
 heat therapy 77
 iron 77
 mortality rate 75
 NFB 75
 phenobarbital 77
 prevention 77
 streptomycin 76
 sulfadiazine 76 77
 symptoms 75
 terramycin 198 199 201
 thyroid extract 77
 transfusions of whole blood 77
 Buboes
 plague 99
 tularemia 78 79
 Buro's solution 111
 Burow-Buschke disease 141
 n Butyl alcohol 603
 Cachexia in histoplasmosis 135
 Cade oil of 678
 Caffeine
 barbiturate poisoning 605
 carbon monoxide asphyxia 597
 cardiac decompensation 444
 cerebral arteriosclerosis 634
 diphtheria 313
 epilepsy 658
 headache 630 638
 relapsing fever 156
 Caisson disease 594-595
 Calamine
 eczematous contact dermatitis 683
 pruritus ani 685
 psoriasis 679
 serum sickness 587
 tinea glabra 674
 tinea manus 676
 Calc um
 angioneurotic edema 584
 hyperparathyroidism syndrome 391
 osteomalacia 560
 osteic acid poisoning 321
 urticaria, 584
 vitamin D 299 301
 Calcium benzyl succinate 111
 Calc um carbonate
 osteitis deformans 558
 paracercariasis chronic 365
 peptic ulcer 326 331
 Calcium chloride
 alimentary tuberculosis 335
 black widow spider bite 617
 colitis chronic thrombo-ulcerative 340
 glomerulonephritis acute 513
 hypoparathyroidism 273
 lead poison 615
 sprue 308
 thrombo-ulcerative colitis chronic 340
 tuberculosis alimentary 335
 Calc um gluconate
 alimentary tuberculosis 335
 atelectasis 378
 black widow spider bite 617
 celiac syndrome, 366

Calcium gluconate—(continued)
 erythroblastosis fetalis, 438
 glomerulonephritis acute 522
 headache 640
 hypoparathyroidism 275
 lead poisoning 615
 palindromic rheumatism 546
 pancreatitis acute 363
 pleurisy acute 384
 preoperative preparation of jaundiced patient 559
 rheumatism palindromic 546
 sprue syndrome 308
 tuberculosis alimentary 313
 uremia convulsive 523
 vitamin D deficiency 501
 Calcium lactate
 headache 640
 hypoparathyroidism 275, 274
 vitamin D deficiency 501
 Calcium mandelate 527
 Calcium pantothenate
 hypertensive vascular disease 452
 neuritis 667
 Calcium phosphate 326, 332
 Calcium propionate 138
 Calcium sulfide 613
 Calculi renal 631
 Calomel
 acute yellow atrophy of the liver 352
 pruritus ani 683
 Camoque 155
 Cantharidin monochromate 665
 Camphorated tincture of opium
 (See Paregoric)
 Cancer of
 oris 160, 318
 Candida albicans 137, 138, 872
 Canicola fever 143
 Cantharic acid 137, 138
 Car sickness 593
 Carbazone
 amebiasis 191
 hepatic insufficiency 356
 Carbolic acid solution 11
 Carbon dioxide administration
 in alcoholism acute 603
 pneumonia 46
 Carbon dioxide freer with in ancylostomiasis 214
 Carbon dioxide-oxygen administration
 atelectasis 377
 hiccough 591
 hyperreflexic syndrome 101
 Carbon monoxide asphyxiation 596, 597
 Carbon tetrachloride
 ancylostomiasis 213
 fluke infections 305
 tapeworm infections 208
 Carbowax 137
 Cardiac arrhythmias 399-405
 auricular fibrillation 402-404
 aminophylline 403
 digitalis 402, 403
 d-lyx 403
 dyspnea 403
 phenobarbital 403
 quinidine 402, 403
 theocaine 403
 auricular flutter 404
 extrasystoles 404
 heart block 401-405
 myocardial infarction acute 421-422
 paroxysmal ventricular tachycardia 400-401
 acetyl beta methylcholine 400, 401
 achlorhydria 401
 atropine 401
 belladonna tincture of 401
 bromides 401
 carotid sinus stimulation 400
 d-lyx 401
 dihydrochloride quinase 400
 spetz syrup of 400
 migraine 401
 morphine sulfate 401
 neostigmine 401
 phenobarbital 401
 prostigmine bromide 401
 quinine 401
 quinine sulfate 400
 secal 401
 strychnine 401
 paroxysmal ventricular tachycardia 401
 aminophylline 401, 402
 coronary occlusion 401, 402
 d-cumaryl 401
 digitalis 401, 402

myocardial infarction 401
 quinidine 402
 Stokes-Adams syndrome 405
 Cardiac catheterization 394-395
 Cardiac contusion 405
 Cardiac decompression 437-448
 Addison's disease 446
 aminophylline 440, 441
 ammonium chloride 440, 441
 arrhythmia 439
 atropine 443
 aureomycin 446
 auricular fibrillation 439
 auricular flutter 439
 barbiturates 444
 bed rest 438, 444
 bronchopneumonia 444
 caffeine 444
 carotid sinus pressure 439
 cedilamide 443, 442, 443
 climate 446
 coramine 444
 covalt 441
 diabetic coma 446
 d-lyx 435, 441, 445, 446, 447
 d-gal 442, 445
 d-lyx 439, 441-443
 tolerance 442
 toxicity 442-443
 digitoxin 441, 442
 d-lyx 441
 d-lyx section aneurysm of the aorta 456
 diuretics 439-440, 444
 edema 439, 441
 electrolyte changes 446
 glucose 444
 gonal 446
 hyperparathyroidism 446
 hypertension 443, 446
 hyperthyroidism 446
 hypoparathyroidism 446
 hypothyroidism 446
 Kartell d-lyx 445
 lassaloid-C 443
 left heart failure 437, 433, 443f
 prevention of recurrent attacks 446
 mercury 444
 mercurial diuretics 439-440, 444
 morphine sulfate 443
 nutrition impaired, 446
 obesity 433
 ouabain 442
 oxygen administration 444
 paroxysmal auricular tachycardia 439
 paroxysmal ventricular tachycardia 439
 penicillin 446
 penicillin constructive 445
 pheochromocytoma 446
 phlebotomy 438
 pneumonia 438
 potassium thiocyanate 446
 propylthiouracil 438
 protopituitary 443
 quinine 439, 443
 rapid ventricular rate 439
 right heart failure 437, 438
 salt restriction, 441, 444
 serum potassium 446
 serum sodium 440
 Smithwick operation 444
 streptokinase 442, 444
 sulfonamides 446
 surgery, 444-446
 tachycardia paroxysmal auricular 439
 paroxysmal ventricular 439
 theobromine 440
 theophylline ethylene diamine 440
 thionin 439
 thionin 438
 thrombosis arterial 438
 thyroidectomy 445
 valvuloplasty 445
 valvulotomy 445
 venesection 446
 xanthine drugs 440
 (See also Coronary insufficiency and Heart disease)
 Cardiac disease in pregnancy
 (See Heart disease)
 Cardiac disease in surgical patient
 (See Heart disease)
 Cardiac trauma, 437
 Cardiospan 328-330
 acetone 318
 belladonna tincture of 318
 disodium 318, 319
 esophageal 316, 317
 esophagectomy 319, 320

gastrostomy 319
 octyl nitrite 318
 Cardiovascular defects congenital
 (See Congenital heart disease)
 Carum of 426
 Carotene 290, 291
 Carotid disease 147
 Carotid fever 157
 Cavernosities in tuberculous 115, 123
 Cecostomy 349
 Cecidant 441, 442, 444
 Celiac syndrome 366-367
 amino acids 367
 brewers yeast 367
 calcium gluconate 366
 d-lyx 367
 diet 366, 367
 gastro-enteritis acute 366
 liver extracts 366, 367
 penicillin 366
 protein hydrolysates 367
 sprue 366
 steatorrhea idiopathic 366
 sulfonamides 366
 vitamins 366, 367
 Cellulohy 347
 Cellulolite, 200, 201
 Cephalalgia
 (See Headache)
 Cerebral circulatory disturbances 626-634
 alcohol 629
 aminophylline 628, 632
 arteriosclerosis 626f
 aminophylline 634
 caffeine 634
 diastolic 634
 hyaline hydrobromide of 634
 nicotinic acid 634
 papaverine, 634
 potassium iodide 634
 quinine sulfate 634
 sodium iodide 634
 theocaine 634
 xanthines 634, 634
 aspirin 630
 barbiturates 632
 benzodrine, 630
 caffeine, 630
 chlorhydrate 632
 clinical pathology 627
 cocaine phosphate, 630
 dextrose 632
 d-lyx 629
 edema 632
 embolism 626f
 Horner's syndrome 631
 prevention 630
 procaine hydrochloride 631
 stellate ganglion block 631
 surgery 631, 632
 ephedrine 630
 epinephrine 630
 ergotamine tartrate 630
 headache 629-630
 hemorrhage 628
 magnesium sulfate 632
 mebutal 630
 nursing care 633
 opium 630
 oxygen administration 632
 papaverine 632
 phenobarbital 628, 630
 physiotherapy for hemiplegia 633
 putitin 630
 renopathy 628
 serum albumin solution 632
 sodium amylal 630
 spinal puncture 632
 sucrose 632
 sympathetomy 628
 thrombosis 626f
 tobacco 629
 treatment general 632-634
 venesection 628, 632
 Chagas disease
 (See Trypanosomiasis, South American)
 Chancroid infection 75
 Chaparral armigerus, 192
 Chaulmoogra oil 100
 Chelonia, 296, 339
 Cheopodum
 ancylostomiasis 213
 ascariasis 210
 Chiclepor 10
 Cholesterol 191
 Chloral hydrate
 angina pectoris 411
 cerebral circulatory disturbances 622

chickenpox menigitis 16
colic functional disorders of 346
coronary insufficiency 411
glomerulonephritis acute 512
influenza menigitis 52
measles encephalitis 13
ricketsal diseases 145
uremia 523 524
Chloramphenicol
(See Chloramycetin)
Chloroquine diphosphate 193 194
Chloresium 569
Chloroquine 154
Chloroform
eczema nummular 683
eructus 666
Chloramycetin
acute bacterial endocarditis 429
amebiasis 193
arthritis brucellar 548
articular infections 543
bacillary dysentery 96
calculi renal 531
cystitis 531
diverticulitis 348
endocarditis acute bacterial 429
subacute bacterial 424 427-428
meningococcal meningitis 47
eructus 666
pertussis 88
pneumonia 43
putrefaction 9
renal calculi 531
ricketsal diseases 146
salmonellosis 92 93
subacute bacterial endocarditis 424 427 428
typhoid fever, 89 90 92
Chloroquine
malaria 153 154
pulmonary abscess 383
Cholangitis 245
Cholecystectomy 245
Cholecystitis acute 360-361
Aerobacter aerogenes 361
artricularitis 361
alkalinization of urine 361
amniotic acid 360
amphibol 360
anemia hemolytic 361
antemycetin 361
blood count 361
cholesterol 360
cholesterol 360
demerol 361
dihydrostreptomycin 361
Eberthella typhosa 361
ferrous sulfate 360
fluid intake 361
glucose 360
insulin 360
liver extract 360
menadione 360
morphine 361
penicillin 361
protein intake 360
Salmonella 361
streptomycin 361
Sulfadiazine 361
sulfamerazine 361
sulfathiazole 361
syndamin 360
transfusion of whole blood 360
chronic noncalculous 361 362
Cholera 98 98
cholera 98 98
barb tarates 98
care of patient 98
convalescence 98
dextrose 98
fluid intake 97 98
glucose 98
morphine 98
prevent on 98 97
sodium bicarbonate 97 98
sodium chloride solution isotonic 97 98
sulfadiazine 98
sulfaguanidine 98
sulfonamide formaldehyde compound (6257), 98
thiamine chloride 98
vacine 97
Cholesterol 408 452
Choline
angina pectoris 408
arteriosclerosis obliterans 461
cholecystitis, acute 360
cirrhosis of the liver 352-353

coronary insufficiency 408
brachycephalus 423
hepatic insufficiency 355 356
hepatitis toxic 350
preoperative preparation of jaundiced patient 357 358
thrombocytosis obliterans 461
yellow fever 35
Chowen 65 70
Chromic gonadotropin hormones 283 285 286 287
Cholesterol 15 157
Chronic acid 314
Chronic sulfuric acid 641
Chronic noncalculous cholecystitis (See Cholecystitis chronic noncalculous)
Chronic thrombo-ulcerative colitis (See Thrombo-ulcerative colitis chronic)
Chronic valvular disease (See Valvular disease chronic)
Chrysarobin 679 680
Chrysotherapy (See Gold therapy)
Cinchona 68
Cinchophen 553
Circulation of the liver portal 352-355
alcoholism, 353 354
amniotic acid 353
arthritis 354
bed rest 352
brewers yeast 353
cholesterol 352 353
diet 352
esophageal varix, bleeding 354
glucose 354
hematemesis 354
liver extract 353 354
typhoid fever 353
prognosis 353-354
vitamins 353
Clitric acid 561
Coal tar
agranulocytosis caused by 439
eczema atopie 682
nummular 683
eczematous contact dermatitis 653
hemolytic anemia caused by 485
pruritus ani 655
psoriasis 680
Calcification of the aorta 397 398
Coccidioid 134
Coccidioidomycosis 134-135 195
antimony 135
bed rest 134
blastomycosis 134
coccidioidin 134
codeine 134
erythema nodosum 195
ethyl iodide inhalation 134
gentian violet 135
immunotransfusion 135
iodine 134
lobectomy 135
penicillin 135
pneumothorax 135
potassium iodide 134
potassium tartrate 135
primary pulmonary type 134
progressive type 134 135
roentgen therapy 135
rubiculites 134
surgery 135
thrombocytosis 135
thyroid 135
vaccine 135
vitamins 134
Codeine
arthritis rheumatoid 540
black widow spider bite 618
bronchiectasis 372 373
bronchitis chronic 372 373
coccidioidomycosis, 134
colic functional disorders of 346 347
common cold 1 2 3
cystitis 529
dengue fever 34
dysenteria 280
epidemic 74
foot and mouth disease 36
gout acute simple exogenous 321
gout 553
headache 630 638 639 644 646
hepatitis 88
influenza 5
infectious mononucleosis 491
karyopsis 368
Köster's syndrome 387

measles 13
mononucleosis infectious 491
mumps 14 15
neuritis 667
osteoarthritis 544
peptic ulcer 327
pericarditis acute 432
pertussis 87
phlebotomus fever 35
pleurisy acute 354
pneumonia 46
psittacosis 7
relapsing fever 156
ricketsal diseases 146
subarachnoid hemorrhage 636
thrombocytosis obliterans 463
thyroiditis acute 271
tracheobronchitis acute 369 370
uremia genuine 523
yellow fever 35
Colchicine
gout 552 553 554
rheumatic fever 66
Cold common (See Common cold)
Colotomy 341
Colitis chronic thrombo-ulcerative (See Thrombo-ulcerative colitis chronic)
Colitis regional ulcerative (See Regional ulcerative colitis)
Collapse of the lung (See Atelectasis)
Collapse therapy in tuberculosis 110 111 115 119 120 123 125 127 128
Colocolostomy 335 343
Colon functional disorders of 344 348
anal spasm 346
atropine 345 347
bed rest 345 347
belladonna extract of 345 347
bromides 346
carbamide 346
cellophyl 347
chloral hydrate 346
codeine sulfate 345 347
colostomy 343 349
coprostasis 344 346
defecation 344 346
diarrhea 344 347
diet 346 348
enemas 346
etiology 344 345
exercise 345
fecal impact on 346
glucose 347
heat to abdomen 345 347
hemorrhoids 346
hypernatremia 344
laxatives 346
methylcellulose 347
mucus in feces 344
phenobarbital 345 347
psychologic factors 347
regulation of intestinal function 346
secalin 346
suppositories glycerin 346
Common cold 1-4
antihistamines 3
aspirin 1 4
autism 3 4
bed rest 1
bronchitis 4
codeine 1 2 3
cough 1 2
diet 1
fever 1
larynx 4
nasal obstruction 2 3
otitis media 3
penicillin 3 4
prevent on 4
sneezing 3
sulfonamides 3 4
vaccines 4
vitamins 4
Compound E (See Cortisone)
Congenital heart disease 395-399
arterial venous shunt 395
bed rest 399
cerebral thrombosis 398
coarctation of the aorta 397 398
diphtheria 399
double aortic arch 395
dyspnea paroxysmal 399
endocarditis subacute bacteriemic 399
heparin 399
oxygen 399

Congenital heart disease—(cont. next)
 patent ductus arteriosus 396
 pulmonary stenosis 396-397
 surgery 395, 396, 398
 venous arterial shunt, 396
 Congenital pulmonary stenosis 396-397
 Conunctivitis
 hay fever 570
 megalococcal 50
 terramycin 201
 Contact dermatitis 344, 346, 347, 409
 Convalescent serum
 chickenpox 14
 leptospirosis 143
 measles 12
 measles encephalitis 13
 mumps 15
 psittacosis 7
 scarlet fever 64, 66
 Cooley's anemia 483, 484
 Copper in hypochromic anemia 483
 Copper salt poison ng 372
 Copper sulfate
 actinomycosis 130, 132
 blas omycosis 133
 Coram ne
 arsenic poisoning 610
 alcoholism acute 601
 barb tarate poison ng 605
 carbon dioxide asphyxia 597
 cardiac decompression 444
 Coronary atherosclerosis
 (See Atherosclerosis of coronary arteries)
 Coronary insufficiency with angina pectoris 408-413, 435-436
 alcohol 410
 amorphous 411, 412
 amyloidosis 411
 anemia 408, 409
 angina pectoris 408, 410, 411, 412
 appendicitis 409
 atherosclerosis of coronary arteries, 408
 409, 411
 bed rest 410
 bromides 411
 chloral hydrate 411
 cholesterol 408
 cholestyramine 408
 cold air danger of 409
 constipation 409
 diabetes 408
 diet, 410-411
 erythromycin 411
 exophthalmos 409
 gallbladder disease 409
 gallstones 409
 glucose 411
 hiatal hernia 409
 hyperlipemia 408, 411
 hypertension 408, 411
 hyperthyroidism 409
 kidney stones 409
 laxatives 411
 lipids 408
 mannitol hexaphosphate 411
 myocardial ischemia 410, 411
 in trophic 411, 413
 obesity 408, 409
 papaverine hydrochloride 412
 peptic ulcer 409
 phenobarbital 411
 potassium iodide 408
 prevention of 408
 propylthiouracil 412
 prostate hypertrophy of 409
 sodium salicylate 411
 strabismus 409
 surgery, 409-410, 412-413
 surgical path 435, 436
 sun 409
 tachycardia 408, 411
 testosterone propionate 412
 theobromine calcium salicylate 412
 thiouracil 412
 thyrotoxicosis 412
 tobacco 410
 tumors malignant 409
 vitamin E 412
 xanthine drugs 411-412
 (See also Myocardial infarction)
 Cortisone
 Addison's disease 238, 589
 agranulocytosis 590
 anaphylactoid reactions 590
 arthritis rheumatoid 533, 541, 542
 asthma bronchial 531
 colitis ulcerosa 590
 dexamethasone 590
 disseminated lupus erythematosus 197

dosage 590
 hypernatremia essential 590
 infectious diseases, acute 590
 nephrotic syndrome 590
 peritonitis nodosa 458
 rheumatic fever 69
 scleroderma 472
 uremia and colitis 590
 (See also Adrenal cortical extract)
 Cressat 441, 670
 Cretinism
 (See Temporal arteritis)
 Cretinism 269
 Croup tent 13
 Cryptitis 340
 Cryptococcus 141, 142
 Cryptococcus neoformans 141
 Cryptorchidism 283
 Curare
 multiple sclerosis 650
 myasthenia gravis contraindicated in 565
 osteoporosis, 559
 parkinsonism 652
 tetanus 102
 Curettage in menorrhagia, 278, 279
 Cushing's syndrome 247, 248, 590
 Cutaneous anthrax 103, 106
 Cyclopropane 436
 Cystitis 529, 531
 cystic acid 530
 acriflavine 530
 aureomycin 531
 Bacillus proteus 531
 Bacillus pyocyaneus 531
 barb tarate 529
 bed rest 529
 belladonna tincture of 529
 boracic acid 530
 chloromycetin 531
 codeine 529
 fluid intake 529
 heat therapy 529
 hyoscynamine tincture of 529
 interstitial 530
 mandelamine, 530
 mandelic acid 530
 naphthol 530
 methenamine 530
 morphine 529
 neomycin 530
 opium suppositories 529
 penicillin 529, 530
 phosphoric acid 530
 polymyxin 531
 potassium permanganate 530
 procaine 529
 silver nitrate solution 530
 Streptococcus faecalis 530
 streptomycin 530
 Suby's solution 530
 sul ad azine 529
 sulfamides 529
 sulfasalazine 529
 sulfathiazole 529
 tuberculous 530
 Daxalin ointment 674, 682, 685
 Deafness
 Ménière's syndrome 669, 670, 671
 osteitis deformans 538
 streptomycin caused by 52
 syphilis 185
 tinnitus 80
 Debilitated in atomic radiation injuries 508
 Decholin
 cholecystitis chronic noncalculous 362
 brachy 641
 Decongestant on disease 594, 595
 Delirium tremens, 601
 Dematitis paronychia
 (See Paronychia)
 Demerol
 arteriosclerosis obliterans 463
 arthritis rheumatoid 540
 cholecystitis, acute 361
 dissecting aneurysm of the aorta 456
 headache 639
 herpes zoster 11
 head poison ng 615
 peptic ulcer 327
 polycystitis acute 30
 subarachnoid hemorrhage 636
 tetanus 101
 thromboangiitis obliterans 463

Dengue fever 34
 Dermal leishmaniasis 160
 Dermatitis herpetiformis 677-678
 Dermatophytosis in syphilis, 163
 Desferrioxamine, 675
 Desferrioxamine acetate
 Addison's disease 256, 257, 258, 259
 orthostatic hypotension 457, 458
 Desoxyephedrine
 alcoholism acute 601
 barb tarate poison ng 605, 607
 narcolepsy 660
 Dextrose
 alcoholism acute 601
 alcoholism acute 601
 epilepsy 658
 narcolepsy 660
 obesity 147
 parkinsonism 652
 Dextrose
 alcoholism acute 601
 barb tarate poison ng 608
 cerebral circulatory disturbances, 632
 cholera 58
 colitis chronic thrombo-ulcerata 337
 340
 diphtheria 83
 methyl alcohol poison ng 603
 myocardial infarction acute 417, 418
 422
 pertussis, 87
 pneumothorax spontaneous 385
 thrombo-ulcerative colitis chronic 337
 340
 (See also Glucose)
 Diabetes insipidus 251, 253
 diet 251
 distress 253
 pituitary 251
 posterior pituitary medications 251
 252
 salt restrict on 251
 Diabetes mellitus 228, 218, 243, 255, 259
 317, 408, 422, 446, 461
 acetaminophen 231, 232, 235, 236
 allergic reactions in insulin 240-241
 arteriosclerosis obliterans 461
 blood sugar levels control by insulin 226, 227
 cardiac disease 236, 408, 422, 446
 contact states 233, 235
 complications acute 230-235
 chronic 235, 241
 desensitization to insulin 240, 241
 diet 218, 223, 224, 231, 232, 233
 emergency management 231, 233
 esophagus 317
 gavage 237
 glomerulonephritis 237
 glucose 230, 231, 232, 241
 ketonuria 243
 infection, 231, 238, 239
 insulin allergic reactions to 240-241
 insulin atrophy 240
 insulin requirements, 223, 229
 globulin insulin with zinc 235
 injection 225
 labile diabetes 228, 229
 moderate diabetes 228
 protein metabolism insulin 223
 severe diabetes 227, 228
 unmodified insulin 224-225
 insulin shock 229, 230, 231, 233
 diagnosis 230
 epinephrine 230
 glucose 230, 231, 233
 symptoms 230
 treatment 230
 Iodine, 240
 mild type 218, 223
 calorics 219, 223
 carbohydrate-fat ratio 219, 223
 desaturation 218
 diet 218, 223, 224
 weight reduction 223
 myocardial infarction acute 422
 ocular complications 236-237
 polyarthritis 236
 premenstrual states 233, 235
 pregnancy 241
 status 237
 low blood emergency management 237
 233
 sugar tests for 232
 sodium iodide 239
 surgical interference 251
 thromboangiitis obliterans 461
 trauma 231
 subcutaneous, 225, 239
 urinary tract infections 239

- vacular disease 236
vitamin B deficiency 293
xanthomas 240
- Dermatosis
leishmaniasis 158 159 160
trypanosomiasis African 161
- Dermatomyoarteriosclerosis obliterans 462
lower nephron neprosis, 526
multiple sclerosis - 648
sudden arterial occlusion 467
thromboangitis obliterans 462
- Diazepam 100
Dibutyl phthalate 145
Dicumarol
arterial occlusion sudden 467 468
arteriosclerosis obliterans 461
endocarditis subacute bacterial 478
multiple sclerosis 649
myocardial infarct on acute 419 420
 421 422
paroxysmal ventricular tachycardia 403
phlebothrombosis 475 427
pulmonary embolism 380 381
thromboangiitis obliterans 461
thrombotic thrombocytopenia III
vitamin K, 305
- Diethylene glycol monoethyl ether 137
Diethylstilbestrol
anorexia nervosa 312
menopause 362
miscarriage 378
mumps orchitis 15
osteoporosis 539
Bile necrosis of the liver acute
(See Acute yellow atrophy of the liver)
- Diffuse scleroderma
(See Scleroderma)
- Digalen 442, 444
- Digitalis
auricular fibrillation 403
auricular flutter 404
cardiac decompensation 439 441-443
 436
congenital heart disease 399
diabetes mellitus 235 236
dissecting aneurysm of the aorta 456
glomerulonephritis chronic 521
heart block 405
hyperthyroidism 262 264 266
lower nephron neprosis 526
myocardial infarction acute 422
myocarditis acute 431
nutritional edema 313
paroxysmal auricular tachycard 401
paroxysmal ventricular tachycardia 401
 402
pericarditis chronic constrictive 433
pneumonia 43
Pregnancy in heart disease 434
rheaping fever 156
rheumatic fever 69
susceptible patient with heart disease 435
syphilis cardiovascular 173
tachycardia paroxysmal auricular 401
tachycardia paroxysmal ventricular 401 402
uremia genuine 522
- Diphtheria
auricular fibrillation 403
cardiac decompensation 441 442
glomerulonephritis chronic 521
myocardial infarction acute 422
- Diphenhydramine HCl
Dipyridamol
hydrochloride quinine 400
Hydroxyergotamine me, 638
- Dihydrostreptomycin
bacillary dysentery 96
haemuria tuberculous 129
beccellosis 76
cholecystitis acute 361
diverticulitis 348
medullary adenoma 389
pertussis 88
tuberculosis alimentary 335
 pulmonary 117
tuberculosis bacillaria 129
tuberculosis meningitidis 62
- Dihydratochrysol
hypoparathyroidism 273, 274
scleroderma 472
sprue syndrome 308
- Dipotassium dihydrophosphate 564
Disinfectants 634 635 636, 637
Distal
arteriosclerosis obliterans 463
dissecting aneurysm of the aorta 456
herpes zoster II
- Mitral regurgitation on acute 418
thromboangitis obliterans 463
Dimethyl phthalate 55
Dinitrophenols 509
Dioxonium 191
Diodes
subacute bacterial endocarditis 426
subarachnoid hemorrhage 635
- Do-oxygenin 282
Dioxydimethoxybenzoin 160
Diphtheria 80-84 322, 405
adrenalin chloride solution on 83
ammonium acid solution isotonic 83
antigenes 81 82
antitoxins, 80 82 83
Arthus phenomenon 83
ascorbic acid 83
bed rest 83
caffeine 83
carrers 84
complications 85-84
dehydration, 83
desensitization on 83
destruc-tion solution on 83
diet 83
electric suction apparatus 83 84
gastritis acute hematemesis 322
garbage tube 84
heart block 405
immunisation 80 81
iron 83
laryngeal type III
oxygen tent 84
penicillin 80 81 83 84
serums vaccinee 81 82
sterilizing 83
proteolysis 83
prophylactic care of patient 82
respiratory therapy 84
Schick test 80 81 84
sulphonamides 83
tetanus toxoids 80 81 III
throatomy 84
vaccine 80
virulence test 84
vitamins 83
- Diphtheria toxin antitoxin serum stock
 acid 385
Diphylophosphoric acid 207 208
Dipyldione calcium 207
- Diamin 162
Dissecting aneurysm of the aorta 455-457
anastomosis 456
atriopeae 456
bed rest 456
cardiac decompensation 456
coagulants 457
demoral 456
diet 456
distals 456
fluids 456
hypertension 457
morphology 455
mortality rate 455, 456
oxygen administration 456
partition 455 456
papaverine 456
surgery 456 457
thrombolytic drugs 456
vitamin C 456
vitamin A 456
- Disseminated lupus erythematosus 196
 197
ACTH 197
anti-thymocyte globulin 196 197
bed rest 196
dianth 196
cardiac involvement 196
coronaries 197
gold colloids 196
penicillin 196
renal involvement 196
stomatodynia 196
sulfonamide des 196
vitamins 196
- Dissiminated sclerosis s 647 651
Ventricular failure 348 349
- Aneurysm 348
bed rest 345
ecstasy 349
cholesteryl ester 348
cobalam 349
diet 348
dihydrostreptomycin, 348
epidemic 346
fibrous 349
glucose 348
hemorrhages 348
infected 348
- Mitral Abbott tube 348
mineral oil 348
neoplasm 349
obstruction colonic 345 349
peri-cell n 345
perforation 349
peptonistis 349
streptovirgin 349
sulfoxur d ne 348
surgery 349
- Dolanine
arteriosclerosis obliterans 463
multiple myeloma 510
thromboangiitis obliterans 463
- Dorvil, 639
Double aortic arch 398
Dracunculus medietensis 117
Drug abuse
leukemia, chronic granulocytes 494
motion sickness 393
- Driscoll 299 302
Duodenal ulcer 317
Dysentery
(See Bacillary dysentery)
Dysenteries, flagellate
(See Flagellate dysentery)
Dysmenorrhea 379 281
aspirin 280
atropine 280
cocaine 280
ephedrine 280
exercise 280
sedative 379 281
pregnancy 281
presacral neurectomy 280
psychomotor factors 280
- Ears block 595
Eberithella typhosa 361
Ecchinopsus granulosus 208 209
Eczema atop c 681 682
infantile 681 682
nummular 682 683
Eczema marginatum 674 675
Ecmated dermatitis s 681 683
Ecdematous monilia s 137
Edema syndrome
(See Neuromuscular asthenia)
Electric shock 595 596
Electric shock therapy for hiccough 393
- Elephantiasis
lymphogranuloma venereum Jd
plastic operations for 215
Embolectomy 380 466
- Emetine
amebiasis 191 192 193 194
Buke infections 203
hepatic insufficiency 356
leishmania s 160
pulmonary abscess 383
- Empyema 374-376
abdominal distends 375
acidosis s 254
adrenalectomy 375
aerosol therapy 375
amnophyllite 375
asthma nos 374
asthma 374
barbiturate 375
benzodril 375
bronchitis 375
dynapnea 374 375
epinephrine hydrochloride 375
ephedrine sulfate 375
helium 375
oxygen therapy 375
penicillin 375
prognosis 376
streptomycin 375
symptomatically drugs 375
tyrosine 375
vaccines for asthma and v duals 374
- Empyrina compound
herpes zoster II
mumps 11
- Empyema
aneura 388
antibiotics 387 388
antimonics s 388
asthma bronchiopleural 387
pneumonia, 46
Exophthalmos lebergica 391
Esophageal stenosis measles 13
Endocarditis acute bacterial
(See Acute bacterial endocarditis)
Endocarditis, subacute bacterial
(See Subacute bacterial endocarditis)
Endocrine factors in obesity 247

Endophthalmitis in meningococcal meningitis 30
 Ensel 681
 Enteric fever
 (See Salmonellosis)
 Enteritis regional
 (See Regional enteritis)
 Enterobiasis 210-212
 diarrhea 211
 enemas 211
 gentian violet 211
 nausea, 211
 phenothiazine 211 212
 prevention 212
 verruca 211
 Enterococci 424
 Enterogastroenteritis 326
 Eparsens 160
 Ephedrine
 angioneurotic edema 584
 asthma bronchial 578 579
 barbiturate poisoning 607
 dysmenorrhea 250
 emphysema 475
 hay fever 570
 headache 630 635 647
 heart block 405
 myasthenia gravis 564
 narcolepsy 660
 poliomyelitis acute 30
 rinitis allergic 574
 urticaria 584
 Epidemic louse-borne typhus 143 144
 Epididymitis inguinalis 674
 Epididymocystitis 129
 Epididymitis tuberculous 129
 Epididymovaginitis 284
 Epilepsy and the convulsive state 655
 359
 alcohol interdicted 654
 amphetamines 618
 arsenic 655
 avertin 655
 barbiturates 655 656
 caffeine 655
 continuous medication 655
 dehydration therapy 658
 desferaline 658
 dilatant sodium 655, 656 657
 ether 658
 fls autonomic discephalic 658
 flur states 658
 glucose 658
 lithium acid 658
 grand mal 655 656 657
 histamine desensitization 658
 ketogenic diet, 658
 magnesium sulfate 658
 mephobarbitol 656 657
 mevantoin 655 656 657
 metrazol 655
 paraldehyde 657
 paraldehyde 654
 pilocarpine 655 657 658
 phenobarbital 656 657 658
 phenothiazine 655 656 657 658
 salt restriction, 655
 sodium amytal 655
 sodium bromide 658
 stasus epilepticus 658
 tridione 655 656 657
 vitamin B complex 658
 Epinephrine
 Addison's disease 259
 angioneurotic edema 584
 arsenic poisoning 610
 asthma bronchial 578 579 580
 emphysema, 475
 erythromelalgia 470
 hay fever 570
 headache in cerebral circulatory disturbances 630
 heart block 405
 insulin shock 230
 orthostatic hypotension 457
 serum sickness 583 584 587 588
 tetanus, 103
 urticaria 584
 (See also Adrenalin)
 Fibro-spiral epaxial paraplegia 285
 Fibrosarcoma 638
 Finasterol irradiated 337
 Ergot, thrombocytopenic purpura caused by, 509
 Ergotamine tartrate
 acute yellow atrophy of the liver 357
 headache 630 637, 639 641

hypersensitization syndrome 391
 Incontinentia ani 550
 Fronto-interventricular blastomycetia 117
 Frysipelas 109 200
 Erythema multiforme 677
 Erythema nodosum 195 196
 erythrasma 196
 bed rest, 195
 coccioidomycosis 195
 etiology, 195
 heat therapy 196
 pyribenzamine 196
 regional ulcerative colitis 344
 rheumatic fever, 195
 sulfhydryls, 196
 sulfonamides 195
 tuberculosis 195
 Erythronalgin
 (See Erythromycin)
 Erythritol 411
 Erythroblastosis fetalis 485-488
 calcium gluconate 488
 electrolytes paternal, 488
 glucose 488
 heparin 487
 oxygen administration 488
 pathogenesis 486
 transfusion 486, 487, 488
 vitamin K, 488
 Erythromelalgia, 470 471
 acetylsalicylic acid 470
 alcohol injection into nerves 471
 climate 470
 epinephrine hydrochloride 470
 roparogen therapy 470
 sympathetomy 471
 temperature warm environmental 470
 Escherichia coli 43 190 202 303, 322
 527 528
 Escherichia histolytica 190 192, 202
 Escherichia nana 190
 Esophageal varices in esophagitis, 316
 317
 Esophagitis, 316 317
 appendicitis 317
 arteriosclerosis 317
 belladonna tincture of 316
 bours 317
 burns 317
 cardiophrenic 316 317
 chylitis 317
 diabetes mellitus, 317
 diet 316
 duodenal tube 317
 duodenal ulcer 317
 echinostoma 317
 ethyl aminobenzoate 316
 gastrostomy 317
 glucose 317
 hiatal hernia 316 317
 ice administration of 316
 phenobarbital 317
 spasm, esophageal 317
 stenosis of esophagus 317
 trauma, chemical 316
 typhoid fever 317
 ulcer duodenal 317
 varices, esophageal 316 317
 Esophagogastricostomy 319, 320
 Estradiol
 breast 640
 menopausal 282
 osteoporosis 559
 Estrogens
 amenorrhea, 277 278
 anorexia nervosa, 312
 breast, 640
 menopausal 282
 menstruation, 278, 279
 osteoporosis 559
 Raynaud's disease 469
 Estroic sulfates
 (See 3-estrone)
 Ether
 asthma bronchial 580
 epilepsy, 654
 intravenous
 arteriosclerosis obliterans 465
 thromboangiitis obliterans 465
 surgical patient with heart disease, 436
 Ethyl aminobenzoate 316
 Ethyl chloride
 freezing warts in ancylostomiasis 214
 hemorrhoids 11
 Ethyl iodide
 angiomatosis 140
 blastomycosis 133
 coccioidomycosis progressive, 134
 necrotic, 143

monilia, 139
 sporotrichosis 142
 Ethyl stibamine 158
 Eucalyptol 646
 Euresol 678 680
 Eucrocin blastomycosis, 141
 Ewald tube 328
 Euphratic colic 409
 Euphorbia
 bronchitis 373
 bronchitis chronic 375
 pulmonary abscess 383
 tracheobronchitis, acute 369
 Extrah 478
 Extravascular, 404 423
 Facial palsy 668
 Famure edema 313
 Fasciitis in scurvy 667
 Fasciolopsis buski 205
 Fecal inspection 346
 Ferric chloride, 521
 Ferric hydroxide 610
 Ferrus sulfate
 anemia, 131 278 308 312, 315, 360
 383
 poorly prepared preparation of laundried
 patient 344
 (See also from therapy)
 Fever therapy
 arthritis gonorrheal 74
 chemotherapy 336 337
 asthma bronchial 331
 multiple sclerosis 648
 Reiter's disease 197
 syphilis, 160 161 162
 Fibrositis 298 336 337
 Filariasis 214 215
 anthelmintic 215
 antimongolia, 215
 arsenic 215
 eosinophilia 215
 helminth 215
 leukocytes 215
 lymphadenitis 215
 lymphangitis 215
 osteomyelitis 215
 prevention 215 216
 types, 216
 Filicaria bancrofti 216
 Filicaria malaya 214
 Fistula, bronchopulmonary 387
 gastric 330
 perianal 340 341
 Flagellate dysentery, 194 195
 Balantidiasis 194 195
 atabrine, 195
 balantidium coli 194
 benzyl benzoate, 195
 bougie solution 194
 oral therapy 195
 quinine, 194 195
 silver nitrate solution 195
 gardians 194
 trichomonas 195
 Flocculation tests for syphilis 165, 166
 Fluke infections 205 207
 (See Schistosomiasis)
 Folic acid
 agranulocytosis 489
 anemia 307, 479, 491, 492
 celiac syndrome 367
 pancreatitis chronic 365
 spina syndrome 305
 Foot and mouth disease 36
 Fournier's gangrene
 (See Fournier)
 Framboesia tropica
 (See Tropical treponematosis)
 Fyfe antigen in lymphogranuloma venereum 36
 Fred Ander's pneumonia 200
 French's syndrome 286
 Fused
 angiolymphoma 214
 granuloma inguinale 167
 histoplasmosis 136
 leishmaniasis, 160
 schistosomiasis 206 207
 Fuchsin
 bacterial
 (See Bacterial fuchsin)
 Fungus disease 130 143
 Furunculosis, 201
 Furunculosis 314
 G. solution, 531
 Gallstones 364 366 400 555

- Calvarization in neuritis 667
Gamma globulin
hepatic insufficiency 355
hepatitis 37 350
measles 12
mumps orchitis, 15
rubella 14
Gangrene 237 464-465
Gastritis 44
Gastric ulcer 317
Gastrotomy 321-324
acute 321-322
 retrograde 321 322
 exogenous simple 321
 hematomatous 322
 phlegmonous 322
chronic 322 324
 atrophic 322-323
 diet 324
 hypertrichic 323
 postoperative stomach 323
 recurrent superficial 322
 syphilis of stomach 324
 Hypertrophic antral 323
 peptic ulcer 323
Gastrocolic fistula 330
Gastro-enteritis acute 36 37 366
 atropine 36
 belladonna 36
 bismuth subcarbonate 36
 celiac syndrome 366
 diphtheria 36 37
 diet 36 37
 glucose 37
 iodine 36
 morphine 36
 opium 36
 paregoric 36
 symptoms 36
Gastro-enterostomy 330
Gastrotomy 317, 319 359
Gaucher's disease 488
Gavage tube
 diphtheria laryngeal 84
 measles encephalitis 13
 poliomyelitis acute 27 28
Ge-Herter Heubner's disease
 (See Celiac syndrome)
Gillespie's syndrome 659 660
Genitourinary tuberculosis 128 130
 autonephrectomy 129
 bacilluria without symptoms 129
 cystitis 130
 dihydrostreptomycin 129
 epididymitis 129
 gonorrhea 130
 methylene blue 130
 nephrectomy, 129 130
 penile type 130
 prostatitis 129 130
 testis lateral 129
 unilateral 129
 streptomycin 129 130
Gentian violet
 actinomycosis 132
 cocci osidomycosis 135
 dysentery 205
 geotrichosis 143
 impetigo contagiosa 672
 monilia 135
 pruritus ani 684
 seborrheic dermatitis 678 679
 tinea cruris 674
 tinea pedis 675
 Vincent's angina 314
Geotrichosis 143
German measles
 (See Rubella)
Hant follicle lymphoma
 (See Hodgkin's disease)
Giardiasis lamblia 194 195
Cardiac 194
Giardiasis intestinalis 194
Gingivitis 299
Glottis 134
Glands 107 108
 aureumycin 108
 bed rest 107 108
 chronic 108
 diet 107 108
 epithelioma 107
 myoma scrota 108
 nodules 108
 lymphadenitis 107
 malleus 108
 pneumonic infiltration patchy 108
 potassium iodide, 108
 quinine 108
 serum antibody titer rise or fall in 108
 sodium bicarbonate 107
 sodium iodide 108
 splenomegaly 107
 streptococcus 107
 sulfadiazine 107 108
 surgery 108
 temperature elevation 107
 varicella 108
 vitamin 107 108
Glaucocoma 644
Globin
 lipid nephrosis 525
 nephrotic syndrome 516
Glomerulonephritis acute 512 514
 abrupt stormy type 512 514
 acidosis 513
 alkalosis 513
 ammonium chloride solution 513
 ammonium citrate 514
 anemia 513
 bed rest 514
 calcium chloride solution 513
 calcium gluconate 512
 chloral hydrate 512
 decalcification of kidney 514 515
 diet 514
 diuresis 513
 glucose 513
 heart failure 513
 hypertension 512 513
 iron 514
 magnesium sulfate 512
 mild form 514 515
 molar solution lactate 513
 phenobarbital 512
 potassium acetate 513
 potassium citrate 513
 salt restriction 514
 sodium bromide 512
 sodium bicarbonate 513
 theobromine 512
 vitamin 514
 "water thrust" 515
chronic 515 521
 alcohol 519
 ammonium citrate 520
 anemia 520
 calcium gluconate treatment of 521
 diet 519 520
 digitalis 521
 diphenhydramine 521
 fluid intake 519 520
 hypertension 521
 iron 520
 kidney lesion treatment of 519 521
 potassium thioacetate 521
 protein intake 519
 rest 519
 rice diet 520
 salin 521
 salt restriction on 519
 theophylline 521
 tobacco 519
 vitamin C, 521
 xanthine drugs 521
 subacute 515
Glossitis 359
Glossoc
 angina pectoris 411
 ascosides 255
 acute yellow atrophy of the liver 351
 Addison's disease 258 259
 alkalosis, 255
 anemia hemolytic 485
 asthma bronchial 580
 bacillary dysentery 94
 brucellosis 77
 cardiac decompensation 444
 cholesterol acute 360
 crisis of the liver 354
 cholera 98
 colon functional disorders of 347
 coronary insufficiency 411
 diabetes mellitus 230 231 233 241
 diverticulitis 348
 endocarditis subacute bacterial 476
 epilepsy 658
 erythroblastosis fetalis 488
 esophagitis 317
 gastro-enteritis acute 37
 gastroenteropathy acute 513
 hepatocellular carcinoma 355
 hepatitis 350
 hypertension, 244
 hypoglycemia functional 245
 insulin shock 230 231 233
 leptospirosis 148
 leukemia, chronic granulocytic 494
 lower nephron nephrosis 526
 malaria 154
 meningitis pneumococcal 57
 meningococcal meningitis 48
 moniliasis 138
 nephrotic syndrome 517
 obesity 248
 osteitis 364
 peptic ulcer 517
 pneumonia 46
 pneumococcal meningitis 57
 poliomyelitis acute 27
 preoperative preparation of jaundiced patient 357
 pyelitis 527
 pyelonephritis 527
 sailor's disease 93
 subacute bacterial endocarditis 426
 tetanus 102
 thermal states 592
 thyroid storm 265
 typhoid fever 91
 uremia, genuine 522 523
 (See also Uremia)
Glutamic acid 658
Glycerol
 dermatitis herpetiformis 679
 eczematous contact dermatitis 683
 erythema multiforme 677
 lichen planus 681
 pruritus ani 684
 Vincent's angina 314
Glyceral trimellate
 (See Nitroglycerin)
Glycine 554
Glycogen in preoperative preparation of
 jaundiced patient 357
Gout
 (See Hyperuricemia)
Gold salts thrombocytopenic purpura
 caused by 509
Gold therapy
 arthritis rheumatoid 337 540
 disseminated lupus erythematosus 106
 intermittent hydrarthrosis 550
 Ritter's disease 197
 rheumatism polyarticular 546
 scleroderma 472
 Gonorrhea 130
Gonadotropin hormone
 anorexia nervosa 309
 headache 640
 impotence 286 287
 male sterility 283 285
Gonorrhea 72 75 201
 alcohol 73
 arthritis 74-75
 fever therapy 74
 heat 75
 immobilization 75
 penicillin 74
 prevention 72 73
 sulfadiazine 74
 sulfathiazole 74
 aspirin 74
 codeine 74
 diagnosis 74
 epididymitis 74
 Kahn test 73
 leukopenia 73
 ophthalmia neonatorum 74
 penicillin 73 74
 prevention 72 73
 proctitis 74
 prostatitis 74
 salicylic acid 73
 sulfadiazine 73
 sulfathiazole 73
 terramycin 201
 urethritis posterior 73 74
 volvulus acute in children 74
Gout 550-555 590
 acute attacks treatment of 552 554
 ACTH 551, 553 554 590
 attack free intervals treatment of 552
 552
 bed rest 552
 cardiac decompensation 446
 chronic period treatment of 554
 cricophren 553
 codeine 553
 colchicine 552 553 554
 diet 552, 553 554 556
 glycine 554
 heat therapy 552 554
 laxative period 550 551
 massage 554
 magnesium 639
 morphine 553
 physiotherapy 554
 provocatives 553

Gout—(cont. next)
 salicylates 552
 symptoms 350-351
 tophaceous 554
 Granuloma inguinale 162 163 202
 anthracine 162
 antimony compounds 162 163
 aureomycin 162 163
 d'agnos 162
 d'armin 162
 fusid 162
 neocapsule 162
 podophyl 162
 roentgen therapy 163
 scarlet red ointment 162
 s t z bath 162
 streptomycin 162 163
 surgery 163
 tartar emetic 162
 terramycin 162
 V accen t organ 162
 Graves disease 245
 Guinea worm infection 217
 Guanidine hydrochloride 364
 Hand Christian-Schuler disease 438
 Hartman's solution 340
 Hashimoto's struma 271
 Hay fever 567 571
 am nophylline 570
 ant h stamin nes 570 571
 asthma 569 570
 benzyl 570
 con unctivatus prescrip tion for 570
 ephedrine 570
 ep nophylline 570
 etiology, 567 568
 filters 568
 hyposecretion 568 570
 neosynephrine 570
 pollen extra t formula for 569
 prevention 568
 pyrenezamine 570
 seasonal 570
 Headache 637 647
 acetophenetidin 638
 acetylsalicylic acid 638 643 645
 a b um n solution 639
 a cobol n ect on 641
 allergy 640
 am nophylline 638
 amyl n tra e 639
 ant h stamin nes 647
 antipyrine 638
 atropine solution 644
 benadryl 647
 benzidine 638 647
 bromides 639
 caffeine 638
 calcium gluconate 640
 calcium lactate 640
 cerebral circulatory disturbances 639
 639
 chondroitin sulfuric acid 641
 codeine 638 639 644 646
 cold compress 637
 constipation 640
 decholin 641
 demerol 639
 digital compounds 637
 dihydroergotamine 638
 doryl 639
 ear, irrigating 644
 endocrine disturbance 640
 ephedrine 638 647
 ergobasol tartrate 638
 ergotamine tartrate 637 639 641
 ergotrate 638
 estradiol benzoate 640
 estrogenic substance (placental) 640
 estrogens 640
 eye or g watering 644
 glaucoma 644
 gonadotropin hormones 640
 gout 638
 heat applications 639 641 643 645
 histamine cephalalgia 646 647
 histamine 638 639
 histamine treatment 647
 Hunt's syndrome 644
 atropine 641
 infections 646 647
 intra-ocular inflammation 644
 massage, 642 643 645
 methochol 639
 migraine 637-641
 morphine 639 644
 myositis cervical 645

nasal drip 643 644
 n acin 639
 n troglycerol 639 647
 oxygen administration 647
 papaverine 639
 peptone 640
 phenazone 638
 phenobarbital 639 643
 physostigmine 644
 p locarpine 644
 p tular extract 640
 p tularia 638
 post traumatic 641 643
 procaine hydrochloride 641
 psychomotor stimulation 643
 psychotherapy 640 643
 pyramidal 638
 pyridemine 647
 referred pain 643 645
 salicylate 643
 salicylates 646
 skull trauma 641-643
 sodium amylal 639 643
 sodium glycocholate 641
 sodium trite 639
 spinal puncture 646
 sucrose solution 639 644
 surgery, 641
 sympathectomy 641
 temporal arteritis 645 646
 temperature and bulbar junction disease of 645
 thyrotoxicosis 640
 toxic states 646 647
 xanthines 639
 Heart block 404-405
 (See also Cardiac decompensation)
 Coronary insufficiency and Myocardial infarction)
 Heart disease congenital
 (See Congenital heart disease)
 Heart disease in pregnancy 434-435
 abortion therapeutic 434
 anesthesia 434-435
 bed rest, 434
 delirium 434 435
 digitalis 434
 hysterotomy abdominal 434
 lactation 435
 prenatal care 435
 prenatal care, 434
 quinine 434
 Heart disease in the surgical patient 435
 417
 am nophylline 436
 angina pectoris 436
 auricular fibrillation 436
 cyclopropane 436
 digitalis 435
 distention of stomach postoperative 436
 endocarditis subacute bacterial 436
 ether 436
 hyperthyroidism 436
 myocardial infarction 435-436
 obesity 436
 oxygen administration 435
 quinine 436
 sodium pentobarbital 436
 spinal anesthesia 436
 subacute bacterial endocarditis 436
 thyrotoxicosis 436
 vascular disease chronic 436
 Heart failure
 (See Cardiac decompensation)
 Heart worms 592
 Heart exhaustion 593
 Heart shock 592
 Heart stroke 592
 Heart therapy in acute polymyositis 29
 Heberden's nodes 545
 He therapy
 alimentary tuberculosis 534
 arthritis rheumatoid 537
 tuberculosis 547
 medical and surgical 539
 rheumatic fever 53
 Helium
 a thma bronchial 580
 decompression on disease 595
 emphysema 575
 Hematemesis
 c ribrous of the liver, 354
 peptic ulcer of esophagus 317
 Hematogenous tuberculosis 119 120
 Hematuria
 menorrhageal menorrhagia 50
 pneumococcal meningitis 57

Hemochromatosis 243
 Hemolytic anemia
 (See Anemia hemolytic)
 Hemolytic disease of the newborn
 (See Erythroblastosis fetalis)
 Hemophilus, 506 507
 Hemophilus infections 202
 Hemophilus influenzae 40 42 51 52 53
 54 202 548
 Hemophilus parvus 43
 Hemorrhoids 346
 Hepatitis
 acute sclerosing obliterans 461
 congenital heart disease 399
 erythroblastosis fetalis 487
 myocardial infarction acute 419 470
 421
 pleurisy with effusion 385
 subacute bacterial endocarditis 424
 426 428
 sudden arteriole occlusion on 467 468
 thrombosing obliterans 461
 Hepatic insufficiency 355-357
 abdominal paracentesis 356
 acute 355-356
 amino acids 356
 ammonium chloride of 356
 ascites 356
 bed rest 355
 brewers yeast 356
 bismuth phosphate test 355
 carbarsone 356
 cholera 355 356
 chronic 356
 diet 356
 emetine hydrochloride 356
 gamma globulin 355
 glucose 355
 icteric index 355
 ergotamine tartrate 356
 liver extract 355 356
 methylhydrazine 356
 phlebotomy 478 477
 procaïne 355
 pruritus 356
 pulmonary embolism 380 381
 serum albumin level 355
 surgery 356
 testostosterone propionate 356
 vitamin B 355 356
 Hepatitis acute infectious and acute
 serum 359
 alcohol 38 39
 atropine sulfate 38
 barbiturates 38
 bed rest 38 39
 convalescent stage 39
 diarrhea 38
 diet 38 39
 gamma globulin 37
 glucose 38
 hypoglycemia 38
 icteric stage 38
 liver failure acute 38
 liver lesions 37 38
 opium 38
 penicillin 38
 preicteric stage 38
 prevention 37
 surgery 38
 vitamin B 38
 toxic 349-351
 amgen 350
 antibiotics 350
 B.A.L. 350-351
 bed rest, 349
 bromosulfalea retent on 350
 choline chloride 350
 diet 350
 diethyl ether 350
 fluid intake 350
 gamma globulin 350
 glucose 350
 human serum albumin 350
 hypoproteinememia 350
 icteric index 349
 liver extract 350
 methionine 350
 oxygen administration on 350
 plasma irradiated 350
 protein hydrolysis 350
 serum bilirubin 350-351
 testosterone 350
 vitamins 350
 Hepatomegaly 507
 Herpes zoster 10 11 202 203
 antihistamine 51
 aureomycin 51
 Buro's solution 51

- carbolized calomine solution 11
 codene 11
 demerol hydrochloride 11
 d l lucid 11
 empa compound 11
 ethyl chloride 11
 morphine sulfate 11
 paravertebral block 11
 pituitrin 11
 procaine solution 11
 roentgen therapy 11
 sodium iodide, 11
 sodium salicylate 11
 tetracycline 202 203
 thiamine hydrochloride 11
 thymol iod. 10
 zinc stearate 10
- Heraldic phenomenon in relapsing fever, 156
- Hetraxan
 clonidine 215
 kiazin 216
 onchocerciasis 216
- Hexamethylenamine 527
 Hexestrol 232
 Helyresorcinol
 acyltolosimias, 213
 ascariasis 210
 tapeworm infections 205
- Hicough 392-393
 hioiditis
 hyaline sulfate 392
 belladonna tincture of 392
 electric shock therapy 393
 fright sudden 392
 hydrochloric acid 392
 lamella shock therapy 393
 oxygen-carbon dioxide 392
 phrenic nerve 392
 psychotherapy 393
 roentgen therapy 393
 sedation 392
 sodium amylal 392
 surgery, 393
- Histamine
 angioneurotic edema 524
 arteriosclerosis obliterans 465
 epilepsy 638
 headache 638 639 647
 hyperchlorhydria 320
 hyperchlorhydria 320
 Ménétre's syndrome 670
 multiple sclerosis 649
 neuritis 668
 thromboembolism obliterans 465
 urticaria 584
- Histoplasma capsulatum* 136 348
 Histoplasmosis 135 136
 anemia 135
 asthenia, 136
 cachexia 135
 diagnosis 135
 diet, 136
 fluids 136
 leukopenia 135
 lymphadenopathy 135
 proctitis 136
 pyrexia intermittent 135
 splenomegaly 135
 sulfadiazine 136
 surgery 136
 transfusion of whole blood 136
 vitamins 136
- Hives
 (See Urticaria)
- Hodgkin's disease and allied disorders 495 502
 giant follicle lymphoma 498 500
 lymphoblastoma 498
 lymphocytosis 498
 lymphosarcoma 498 499 501
 mortality rate 498 499
 mycosis fungoidei 501
 neoplasms 499 500 501
 radiophosphorus 499 500
 reticulum cell sarcoma 498 501
 roentgen therapy 499
 surgery 499
- Holistic concept of disease 65
 Hookworm infections
 (See Ancylostomiasis)
- Horse serum in serum sickness 385
 Human hyperimmune globulin 86 88
 Hunter's ulcer 530
 Hunter syndrome 644
 Hydrarthrosis intermittent
 (See Intermittent hydrarthrosis)
- Hydralin 682 685
- Hydrocephalus 50
 Hydrochloric acid dilute
 actinobacillus in pancreatitis 365
 acme 676
 anemia, hypochromic 483
 perniciosis 480
 angioneurotic edema 584
 gastritis chronic atrophic 323
 chronic recurrent superficial 322
 hicough 392
 hypochlorhydria, 321
 osteomalacia 561
 paraplegia in lesions of the spinal cord 662
 urticaria 584
- Hydrogen peroxide
 infections mononucleosis 491
 stomatitis herpetic 315
 Vincent's angina 314
- Hydrotherapy in acute polyomyelitis 29
 Hyk none 306
Hymenolepis nana 207
 Hyoscine
 cerebral arteriosclerosis 634
 motion sickness 593
 myasthenia gravis 564
 parkinsonism 652
- Hyperadrenalism 542
 Hyperalkalemia in hyperthyroidism 275
 Hypercalcemia in hyperthyroidism 276
 Hyperchlorhydria 320 321
 Hypercholesterolemia 515
 Hyperglycemia 590
 Hyperimmune globulin buisus in peritonitis 88 88
- Hyperimmune rabbit serum in bartonella disease 347
 Hyperimmune serum in rabies 21 22
 Hypertension 243 246
 diagnosis 244
 glucose 244
 hypoglycemia functional 244 246
 surgery 244
- Hypertension in coronary insufficiency 408 411
 Hyperparathyroidism primary 275 276
 446, 531
 cardiac decompensation 446
 hypercalcemia 275
 hypercalcemia 276
 renal involvement 276 531
 serum calcium 275
 serum phosphorus 275
 surgery 276
 symptoms 275 276
 tetany postoperative 276
- Hypersthenia 333 344
 Hyperthermia in alkalosis 254
 Hyperthyroidism
 ACTH 590
 anorexia pectoris 408, 411
 cardiac decompensation 445-446
 coronary insufficiency 408 411
 cortisone 590
 dissecting aneurysm of the aorta 456
 glomerulonephritis chronic 521
 myocardial infarction acute 414
 (See also Hyperthyroidism vascular disease)
- Hypertensive encephalic syndrome 449 450
 Hypertensive vascular disease 448 455
 animal protein 452 453
 arteriosclerotic hypertension on 449
 bacterial pyrogens 454 455
 cardiovascular organ on 448 449
 cholesterol 452
 diet 451
 endocrine organs on 448 449
 essential hypertension on 448 449 455
 hypertension arteriosclerotic 449
 essential 448 449 455
 malignant 454-455
 hypertensive encephalic syndrome 449-450
 iron 452
 Keweenaw rice diet, 451-453
 kidney extracts 453-454
 neuroticism 448 449 450
 potassium thiocyanate 451
 prehypertensive individual 449
 protein on 452 453
 pyrogenic bacterium 454 455
 pyrogen on 455
 renal organ on 448 449
 rice diet, 451-453
 salt 454
 salt restriction 451
- Sympathectomy 453
 vitamins 452 454
 (See also Hypertension)
- Hyperthermia 592
 Hyperthyroidism 260-269 409 436 446
 adenomatous goiter, 261 264
 agranulocytosis 263 264 265
 angina pectoris 409
 auricular fibrillation 266
 bed rest 262
 cardiac decompensation 446
 cord paralysis 263
 coronary insufficiency 409
 diagnosis 261
 diet 262
 digitalis 262 264 266
 exophthalmic goiter 261
 glucose 265
 iodine, 261 263 264
 Lugol's solution 261 263 264 265
 methylthiouracil 261 262 264 265
 mild type 261 262
 moderate type 262 263
 myxedema 262 263 268
 phenobarbital 262
 primary 261 264
 propylthiouracil 261 262, 264 265
 266
 radioactive iodine 260 261 263 264
 267 268
 recurrent 263
 relapsing 263 264
 roentgen therapy 263 267
 severe type 263 268
 surgical patient with heart disease 436
 tetany 263
 thiouracil 261 262 264 265 266
 thyrotoxic acid disease 266 267
 thyroid storm 265 266
 thyroidectomy 260 261 262, 263
 264 265 266
 thyrotoxicosis 265
 vitamins 262
- Hyperventilation syndrome 390-392
 adrenal gland overactivity of 391
 ammonium chloride 391
 calcium 391
 encephalitis lethargica 391
 acetaminophen 391
 narcosis 391
 oxygen-carbon dioxide administration 391
 psychoneurotic origin 390/391
 psychotherapy 391/392
 sedation 391
 symptoms 390
- Hypochloremic tetany
 apraxia syndrome 307 308
 vitamin D deficiency 301
- Hypochlorhydria 320 321
 Hypochromic anemia
 (See Anemia hypochromic)
- Hypoglycemia functional 244 246
 acute yellow atrophy 245
 Addison's disease 245
 cholera 245
 cholecystectomy 245
 carbonyl 245
 diet 244 245 246
 glucose, 245
 Graves' disease 245
 hepatic 245
 hypernatremia 245
 hypophyseal cachexia 245
 hypothyroidism 245
 liver disease 245
 metastatic tumors 245
 neuritis 245
 Simmonds disease 245
 sympathetic nervous system disturbance of 246
- Hypogonadism 284
 Hypomagnesemia
 (See Aneurism)
- Hyperparathyroidism 272 275 276 446
 acute 273 274
 amphotel 275
 calcium chloride 273
 calcium gluconate 273
 calcium lactate 273 274
 cardiac decompensation 446
 chronic 274 275
 diagnosis 273
 diet 274 275
 dihydroxycholesterol 273 274
 laryngeal spasm 274
 milk intake 274 275
 parathyroid hormone 273 274
 phosphate 274 275

atabrine 160
 herberine sulfate 160
 cancrum oris 160
 cocaine solution 160
 complications 160
 dermal type 160
 xanthine compounds 158 159 160
 emetine hydrochloride 160
 eparseno 160
 ethyl atabrine 158
 fuad n 160
Leishmania donovani 158
 neocorpamine 160
 neostan 159
 neostibosan 158 159 160
 Oriental sore 160
 pemicilin 160
 penlamidine 159 160
 phenamidine 159
 potassium antimony tartrate 160
 propantholol 159
 seluribosan 158 159
 stibosan 158 159
 stiburea 159
 stibamide 159
 sulfonamides 160
 tartar emetic 158 159 160
 urea stibamine, 159 160
 vacrine 160
 Western mucocutaneous type 160
 Leprosy 100
Leptospira 147 148
Leptospira 147 148
 albuminuria 148
 anisuria 148
 anemia 147
 aureomycin 148
 azotemia 148
 convalescent serum 148
 diet, 148
 glucose, 148
 hypo-albuminemia 148
 oliguria 148
 periculis 148
 plasma, lympholized 148
 prophylaxis 148
 streptomycin 148
 transfusions 148
 types 147 148
 vaccine 148
 vitamin K 148
 Leiffrer-Swe d disease 488
 Leukemia 491 498
 acute 491-492
 amethopterin 491 492
 am-n-o-an fol 491 492
 aminopterin 491 492
 nitrogen mustard 492
 radiophosphorus 491
 urethane 492
 chronic granulocytic 492-497
 arsenic 494
 bed rest 496
 benzene 496
 diet 496
 drainage 494
 glucose 494
 infections 496 497
 myelocytosis 491
 nitrogen mustard 496
 oral hygiene 497
 pyridoxine hydrochloride 494
 radiophosphorus 494 495
 radium 494
 roentgen therapy 491 494
 splenectomy 496
 transfusion of whole blood 497
 urethane 493 495-496
 chronic leukem c reticulo-endothelios 498
 chron c lymphocytic 491 498
 Leukocytosis 348
 Lichen planus 680 681
 Lipemia
 arteriosclerosis obliterans 461
 thrombosis obliterans 461
 Lipocac 405
 Lipoid disorders in diabetes mellitus 240
 Lipoid nephrosis 524 525
 Liquor anemion causticus in neurom 666
 Liquor calici
 dermatitis herpetiformis 678
 ecthyma contact dermatitis 683
 erythema multiforme 677
 pityriasis rosea 680
 pruritus ani 684
 psoriasis 679
 Liquor carbonis detergens
 dermatitis herpetiformis 678

eczematoid dermatitis 682
 lichen planus 681
 pruritus ani 684
 Listeria 601
 L. vesic reticularis 469 470
 Liver, acute yellow atrophy 351 352
 Carcinoma portal 352 355
 Liver extract
 avarantocytosis 489
 anemia 307 308 323 478 479 480
 451 649
 celac syndrome 366 367
 cholestylos acute 360
 cirrhosis of the liver portal 353 354
 gout caused by 353
 hepatic insufficiency 355 356
 hepatitis toxic 350
 pancreatic chronic 365
 pellagra infantile 295
 preoperative preparation of jaundiced patient, 358
 Scherrie c dermatitis 679
 Liver failure
 (See Hepatic insufficiency)
 Liver therapy
 malaria 354
 moniliasis 139
 Lou dog 216
 Louisa 216
 Lobectomy
 actinomycosis 131
 asthma bronchial 381
 coccidiosis mycosis progressive 135
 thyroditis acute 271
 tuberculous pulmonary 115 122 114
 Wolff's syndrome 346 387
 acetylcholinic acid 387
 aerosol therapy 387
 allergens 386
 ancylostomiasis 314
 ankylostomiasis 387
 barbiturates 387
 bromides 387
 codeine 387
 Louse born typhus epidemic 143 144
 Lower nephros nephrosis 525 527
 sodium bicarbonate 526 527
 transfusions 526 527
 Lugol's solution
 actinomycosis 132
 hyperthyroidism 261 261 264 265
 moniliasis 138
 Lymbago 556 557
 Lumpy jaw
 (See Actinomycosis)
 Lupus erythematosus disseminated 590
 Lymphadenitis
 Alarbus 215
 glands 107
 tularemia 78
 Lymphadenoma
 (See Hodgkin's disease)
 Lymphocytoma
 (See Hodgkin's disease)
 Lymphosarcoma
 (See Hodgkin's disease)
 Lyon's method of duodenal drainage 364
 Lymphogranuloma venereum 36 202
 Macrocytic anemia of infancy 481
 Macrocytic anemia of nutritional deficiency 481
 Macrocyt c anemia of pregnancy 470
 Macrocyt c hyperchromic anemias 478
 481
 Madura foot 140 142
 Madaromycosis 140 142
 Magdala rose dye 205
 Magnesia bentonite 681 683 684
 Magnesium chloride 340
 Magnesium extract 213 362
 Magnesium oxide
 (See Milk of magnesia)
 Magnesium phosphate 376
 Magnesium sulfate
 arsenic poisoning 610
 black widow spider bite 67
 cerebral circulatory disturbances 632
 cholestylos chronic noncalcific 362
 epilepsy, 658
 glomerulonephritis 512 515
 influenza meningitis 52
 lead poisoning 322 615 616
 lymphadenitis suppurative 78
 pancreatitis acute 364
 subarachnoid hemorrhage 636
 tapeworm infections 208
 Tetanus 101
 uremia convulsive 523
 Magnesium trisilicate 326 331 358
 Malaria 148 154 155
 anemia hemolytic 485
 aralen 153 154
 arsenic 154
 aspirin 154
 atabrine 151 152
 bismuth 154
 Blackwater fever 154 155
 camoquin, 153
 chloroguanide 154
 chloroquine 158 154
 diet, 154
 etiology 148 149
 glucose 154
 immunology 149 150
 iron 154
 liver therapy 154
 methylene blue 154
 paludic 154
 pamaquin 152
 pentamidine, 152 153
 plasmodium 152
 plasmodia 149 149
 prophylaxis 150
 quinacrine 151 152
 quinine 150 151
 sulfonamides 154
 Malleus 108
Maliomyces pseudomallei 109
 Mandelam ne, 330
 Mandelic acid 530
 Manganol benzenate 411
 Mapharsen
 cystitis 530
 rat bite fever 157
 asplenia, 169 170
 Vincent's angina 314
 Mar e-Sumpell d disease
 (See Arthritis rheumatoid)
 Marsh fever 147
 Measles
 aminopterin 13
 aspirin 13
 aureomycin 13
 borax acid 13
 bronchitis 13
 bronchopneumonia 13
 codeine 13
 convalescent serum 12
 cough 13
 group test 13
 diet 12 13
 encephalitis 13
 eye protection 13
 fever 13
 gamma globulin immune 12
 laryngitis, 13
 of the media 13
 penicillin 13
 prevention 11 12
 sulfadiazine 13
 symptoms 11
 tracheitis 13
 vasoconstrictor drugs 13
 Nebal 656 657
 Netholyl
 acrycyanos 470
 headache 639
 scleroderma 471 472
 Medial nail emphysema spontaneous 390
 Mediastitis acute suppurative 389 390
 abscesses acute 389
 chronic 389-390
 cod liver oil 389
 dihydrostreptomycin 389
 gastrostomy 389
 heliotherapy 389
 penicillin 389 390
 streptomycin 389
 sulfonamides 389 390
 vitamin as 389
 Melchior's 108 109
 antiserum 109
 aureomycin 109
 bed rest 109
 penicillin 109
 potassium iodide 109
 sodium bicarbonate 109
 sodium iodide 109
 streptomycin 109
 sulfadiazine 108
 sulfathiazole 108
 vaccines, 109
 white matter 109

pericarditis acute, 432
 plague 99
 pleurisy acute 384
 pleurodynia infectiosa 197
 pulmonary embolism 380
 relapsing fever 156
 renal calculi 531
 rickettsial diseases 146
 subarachnoid hemorrhage 636
 sudden arterial occlusion 467
 tachycardia paroxysmal auricular 401
 thrombotic phlebitis 463
 thyroid storm 263
 uremia convulsive 524
 yaws 523
 yellow fever 35
 Morphine add. ction 441
 Morphine poisoning 254
 Motion sickness 593
 Moutan sickness 594
 Multiple myeloma 510 511
 Multiple sclerosis 647 651
 anti-infectious treatment 647
 antithrombotic treatment 649
 arsenic 648
 bed rest 649
 eucaria 650
 d. alberti, 648
 dicumarin 649
 fever therapy 648
 histamine 649
 iron 649
 liver extract 649
 malaria treatment 648
 myeloblastin 650
 neocarbazone 648
 physiotherapy 650
 proglutinin 650
 psychotherapy, 650 651
 quinine 649
 relapses 650
 roentgen therapy 649
 silver salivarian, 648
 sympathectomy cervico-thoracic 649
 transfusions of whole blood 649
 urinary infections 649
 vaccines 648
 vitamins 649
 Mumps, 14 16
 acetylsalicylic acid 14 15
 codine 14 15
 convalescent serum 15
 diethylstilbestrol 15
 empirin compound 14
 fever 14
 gamma globulin 15
 mastitis 15
 meningo-encephalitis 15
 neutral 14
 oophoritis 15
 orchitis 15
 parotitis 15
 pharyngitis 14
 prevention 15
 seccal 14
 Mumps typhus fever 144
 Myalgia 195
 Myanema
 anisolemia acute 601
 multiple sclerosis 650
 parkinsonism 652
 Myasthenia gravis 561 566 590
 ACTH 560
 amino acids, 564
 atropine sulfate 562 563 564
 belladonna tincture of 563 564
 choline acetylcholine 564
 d. copropyl fluorophosphate 564
 ephedrine sulfate 564
 guanidine hydrochloride 564
 hyoscine 564
 oxygen administration on 563
 potassium chloride 564
 prostigmine 562 563, 564
 roentgen therapy 565
 thymectomy 564 565
 thymus therapy 564 565
 trichostomy 565
 Mycetozoa 140 142
 Mycosis of the hairless skin 674 676
 Mycosis fungoides 501
 Myeloma, multiple
 (See Multiple myeloma)
 Myelophthisic anemia 482
 Myocardial infarction acute 401 414
 423 435-436
 abdominal distention on 417
 after-care of patient 422 423
 after-care 419

amorphophylline 415 418 422
 ant. coagulants 416 419 421
 atropine sulfate 415 419
 auricular fibrillation 421-422
 auricular flutter 421 422
 bed rest 416-417
 cardiac arrhythmias 421-422
 complications 421-423
 congestive heart failure 421
 digitalization 417
 dextrose 417 418 422
 d. cumarol 419 420 421 422
 diabetes mellitus 422
 diet 417
 d. malis 422
 d. potius, 422
 d. laud. d. hydrochloride 418
 enemas 417
 extrasystoles 421
 fluid intake 417 418
 heparin 419 420 421
 hypertension 414
 morphine sulfate 415 418 422
 nardone d. sulfate 421
 nitrates 419
 obesity 417
 oxygen administration 415 416
 422
 Panipon 418
 Papaverine hydrochloride 415 418
 paroxysmal ventricular tachycardia 401
 phenobarbital 418
 pulmonary congestion 422
 quinidine sulfate 419 421
 shock, 421
 shoulder-hand syndrome 422
 sodium chloride solution 417
 stupor abdominal 417
 surgical patients 435-436
 tachycardia ventricular 401 421
 transducers 421
 vitamins 417 420
 Xanthine drugs 418
 Myocardial ischemia 410 411
 Myocarditis acute of infectious disease 91 162 431
 Myochrysin 538
 Myotitis cervical 645
 Myxedema
 (See Hypothyroidism)
 Naphthalan
 eczema atopic 682
 eczematous contact dermatitis 683
 Napburde sodium 216
 Narcosis 659 660
 Nasal allergy due to fungi 571 573
 asthma 571
 hypopneumatization 572 573
 molds 571
 rhinitis, 571
 tracheobronchitis 569
 Nasopharyngitis
 streptococcal meningitis 49
 myocarditis, acute 431
 Necator americanus 212
 Necrobacillus lipodermatitidis 240
 Necrotizing arteritis 458
 Negro bed sores in males 20
 Nembutal
 Bradycardia in cerebral circulatory disturbances 630
 mumps 14
 Neosphenamine
 amphetamine 105 106
 cystin 550
 granuloma inguinale 162
 leishmaniasis 160
 multiple sclerosis 648
 rat bite fever 157
 Vincent's angina 314
 Neostam
 E. scopolamine 136
 leishmaniasis 159
 Neost. hogan
 Glucosyl 215
 leishmaniasis, 158 159 160
 Neostigmine
 (See Prostigmine)
 Neotomaphysa
 burburensis poison mg 607
 hay fever 570
 orthostatic hypotension 457
 Nephrectomy 129 130
 Nephritis
 (See Glomerulonephritis)
 Nephrosclerosis 590

Nephroses 1 pond
 (See Lipoid nephrosis)
 lower nephron 525 527
 Nephrotic syndrome 515 518
 ascia 516 517
 ACTH 518
 albuminuria 515 517
 amino acids 516, 518
 ammonium chloride 517 518
 ammonium nitrate 518
 diet 515 516
 diuresis 517
 edema generalized 515
 fluid intake 517
 globulin 517
 glucose 517
 hypercholesterolemia 515
 hypoalbuminemia 515
 J. poise in urine doubly refracting 515
 mercurhydride 516 517
 mercaptopurine 517
 mercuraphylline 517
 nephrotic crisis 518
 penicillin 518
 pneumococcal peritonitis 518
 potassium chloride 515
 potassium nitrate 518
 protein hydrolyzates 516
 salt restriction 516 517
 serum albumin 516
 thiomersal urea 517
 thyroid 518
 Nervous system diseases of 619 671
 Nettle rash
 (See Urticaria)
 Neurasthenia 234 293
 Neurolepsy presacral 280
 Neuritis 668 668
 acetylcholinesterase 667
 aureomycin 666
 bed rest 666
 chloroform, 666
 chloromycetin 666
 codeine 667
 colitis regional ulcerative 344
 d. aphoresis 666
 eucalyptol 666
 faradization 667
 galvanization 667
 heat applications, 666
 histamine 666
 iontophoresis 666
 liquor ammoniac caustic 666
 massage 667
 menthol 666
 methacholine 666
 methadon 667
 methyl salicylate 666
 morphine 667
 oleum terebinthinae 666
 paralysis muscular 667
 penicillin, 666
 phenobarbital 667
 potassium iodide 666
 preoperative preparation of jaundiced patient 559
 regional ulcerative colitis 344
 streptomycin contraindicated 666
 strychnine 667
 thymol 666
 vitamins 667
 Neurocirculatory asthenia 405 408
 diet 407
 hypoglycemia 406 407
 infections 406 407
 phenobarbital 407
 psychological factors 406
 rest 407
 symptoms 406
 vitamins 407
 Neurosis in functional hypoglycemia 246
 Neurosyphilis 182 183
 Niacin
 absorption 294
 arthritis 295
 bromide intoxication 609
 cerebral arteriosclerosis 634
 coronary artery disease 295
 fibrinates 295
 headache 639
 hypertensive vascular disease 452
 Ménière's syndrome 295 670
 myalgia 295
 neuritis 667
 nutritional edema, 313
 pellagra 294 295
 requirements, 294
 stomatitis 316
 storage 294

- Parad one 657
Paraffin d ps 535 545
Paraldehyde
Paralysm acute 600 601
Parasitosis infors rat on 609
Paratyphoid 658
rickettsal diseases 145
subarachnoid hemorrhage 636
Paraplegia in lesions of the spinal cord 600 665
acute traumatic 661
alcohol subarachnoid injection of 664
bladder care 662 663
bladder stones 663
catheterization on 663
complications 663
delegation 664
diet 664
enemas 664
fluid intake 662
hydrochloric acid dilute 662
laminectomy 661
muscle spasm 664
nursing care 662
pain treatment of 664
phenobarbital 664
pruritus 663 664
mycobacterium 664
rectal care 664
rehabilitation program 665
spinal block 661
sulfonamides hypersensitivity to 663
surgery 661 662
transfusion of whole blood 662
ulcers decubitus 662
vitamins 662
Parasympathomimetic drugs 25
Parathormone 274
Parathyroid glands diseases of 272 276
Parathyroid hormone 273 274 335
Paratyphoid fever
(See Salmonellosis)
Paratyphoid
bacillary dysentery 94
dysentery
gastroenteritis acute 36
salmonellosis 93
(See also Opium)
Paros of extremities in influenza pneumonia 52
in syphilis 181 183 184
Parkinsonism 651 653
amphetamine 652
arthritis 653
atropine sulfate 652
belladonna 652
belladonna 651 652 653
benzedrine 652
curare 652
dreadnought sulfate 652
dry mouth 652
hypocapnia 652
hypokinesia 651 652 653
myasthenia 652
paraparesis 652
physiotherapy 653
pilocarpine dilute 652
postencephalitic 651 652 653
prostigmine bromide 653
rigidity 651 652
stramonium 652 653
surgery 653
temper 651 653
tired one 653
Paronychia chronic 137
Paroxysmal auricular tachycardia 400-401 439
Paroxysmal ventricular tachycardia 401 402 421 439
Parpanit 652
Parrot's law 120
Parvovirus fulvirens 43
Patent ductus arteriosus 396 429
Pavlov's 665
Pellagra 294 295
Penicillin
actinomycosis 130 131 132
acute bacterial endocarditis 5 429
agranulocytosis 265 489
amebiasis 192
anemia 4 hypoplastic 482
anthrax 105
arteriosclerosis obliterans 464
arthritis gonorrheal 74 547
meningococcal 547
articular infections 548
asthma bronchial 580
atelectasis 378
atomic radiation on joints 598
bartonella disease 147
Bayel 185
blastomycosis 133
bronchiectasis 371 372
bronchitis chronic 371 372
calculus renal 531
cardiac decompensation on 446
cell ag syndrome 366
chickenpox 18
cholecystitis acute 361
common cold 3 4
cryptosporidiosis 141
cystitis 529 530
diphtheria 80 81 83 84
disseminated lupus erythematosus 486
diverticulosis 348
emphysema 375
endocarditis acute bacterial 429
subacute bacterial 424 427
erysipelas 72
leptospirosis acute phlegmonous 322
gonorrhea 73 74
hepatitis 38
histoplasmosis 136
impetigo contagiosa 672
infectious mononucleosis 491
influenza 5
influenzal meningitis 52 53
leishmaniasis 160
leptospirosis 148
lymphadenitis suppurative 78
magnesium 142
measles 13
metastatic acute suppurative 389
390
melo-dosis 108
meningitis influenzal 52 53
meningococcal 47 50 51
pneumococcal 55 56 57
staphylococcal 59
streptococcal 54
mononucleosis infectious 491
hepatic syndrome 51A
neuritis 666
ophthalmia neonatorum 74
pancreatitis acute 564
paratyphoid acute 438
paratyphoid acute 433
pertussis 87
pleurisy 187
pleurisy with effusion 386
pneumococcal meningitis 55 56 57
pneumonia 40 41 42 46
poliomyelitis acute 30
preoperative preparation of jawed 66
pauca 559
proctitis 74
prostatitis 74
psittacosis 89 41
pulmonary abscess 383
pyelitis 521 528
pyelonephritis 522 528
relapsing fever 157
relapsing fever 156 157
renal calculus 531
rheumatic fever 68
ricketsal diseases 146
rheumatism 74
scarlet fever 64 65 66
smallpox 17
smallpox vaccination on 18
streptococcus 142
staphylococcal meningitis 59
sterility male 284
stramonium caused by 315 316
stomatitis gangrenous 315
streptococcal meningitis 58
subacute bacterial endocarditis 424-427
syphilis 164f
thrombocytosis obliterans 464
thrombo-vascular colitis chronic 339
thyroid storm 265
thyroiditis acute 271
thyroiditis spontaneous 187
Vincent's angina 514
volvovaginitis 74
Pentamidine
leishmaniasis 159 160
multiple myeloma 510
trypanosomiasis African 161
Pentamidine 152 153
Pentastemella 489
Pentastemella 616
Peptic ulcer esophageal 317 318
gastric and duodenal 324-332 366
409
acute 326f
aluminum hydroxide 326 327 331
aluminum phosphate 326 331
amberlite 326
ambulant management 329
angina pectoris 409
atropine 336 327 328
benzine 332
belladonna 316 323
bismuth subcarbonate 326
bismuth subnitrate 326
calcium carbonate 326 331
calcium phosphate 326 331
codeine sulfate 327
contraindication 409
diemerol 327
dysentery 325 327
diet 325, 326 328 329 331 332
emotional involvement, 329 330
enemas 327
enterogastrostomy 326
Ewald tube 328
gastrostomy 330
gastric fistula 330
gastro-enterostomy 330
gastrojejunostomy 330
glucose 327
hemorrhage 327 328
jejunostomy 330
kaolin 331
magnesium oxide 326 331
magnesium phosphate 326
magnesium trisilicate 326 331
metabismuth bromide 332
milk of magnesia 326 331
morphine sulfate 327
obstruction 328
obstructive chronic 366
pharyngitis 326 328
perforation, 327 329
protein hydrolyzates 326
pylorospasm 320
retention 328
sodium bicarbonate 326
sodium citrate 376
surgery 327 329 330
transfusion of whole blood 327
vagotomy 330
Vitamin 326
Perniosis nodosa 458
Pericarditis 433
Pericarditis 433-433
acute 433-433
bed rest 433
codeine 432
ice packs 432
influenza 432
meningitis 431
morphine 432
pericarditis 433
pericardial sac tapping of 432 433
pericardial cyst 433
pneumonia 432
rheumatic fever 432
salicylates 432 433
streptococcus 433
tuberculosis 432
chronic constrictive 433
Peritonsillar abscess 344
Peritonsillar abscess in uremia 523
Peritonsillar 137
Peritonsillar
dysentery 349
tetramycin 200 203
Peritonsillar abscess
(See Anemia peritonsillar)
Peritonsillar abscess 201 203
antigen aluminum precipitated 84 85
B. paratyphoid infection 85
bactericidal lamps 87
barbiturates 87
bed rest 85
bronchopneumonia 85
codeine 87
chloromycetin 88
complications 88
convulsions 88
dextrose 87
dysentery 86
diet 86 87
dihydrostreptomycin 88
enemas 85 87
gastrointestinal involvement 86
human hyperimmune globulin 86
hypodermoclysis 87
immunity test 85
immunization passive 86
opium 87
penicillin 87
prevent on 84-85
react on to vaccine 85

- Pertussis---(cont. med)
 Schick test 33
 streptomycin 87 88
 sulfadiazine 87
 tetramycin 202 203
 tetanus toxoids, 84
 tetracycline 86-88
 vaccines 81 82 84 85 86
 vitamin K 86
 Pfeiffer's bacillus
 (See *Haemophilus influenzae*)
 Pharynx in streptococcal 199 200 203
 Phlebotomy 46
 Phlebotomy 139
 Phenazone 634
 Phenobarbital
 angina pectoris 411
 anoxia nervosa 312
 arthritis, rheumatoid 546
 asthma bronchial 581
 auricular fibrillation 402
 bromide intoxication 609
 brucellosis 77
 cerebral hemorrhage 428
 chekropor 16
 colon functional disorders of 345 348
 coronary insufficiency 411
 eczema atopic 482
 epilepsy 656 657 658
 esophagus 317
 extrastyles 404
 gastritis, 322, 323
 glomerulonephritis, acute 312
 heads 650 659 643
 heart block 403
 hyperthyroidism 262
 industrial men 18 32
 intestinal hemorrhage 91
 laryngitis 358
 meninges encephalitis 12
 meningitis pharyngeal 51
 menopausal men 41 47
 menopausal 282
 mumps 14
 myocardial infarction acute 418
 neuritis 667
 neurocirculatory asthenia, 407
 paraplegia in lesions of the spinal cord 46
 paroxysmal auricular tachycardia 401
 peptic ulcer 326 328
 pertussis 111
 pleurisy with effusion 353
 poliomyelitis acute 30
 pruritus 615
 pylorospasm 320
 tachycardia paroxysmal auricular 401
 Phenol
 dermatitis herpetiformis 618
 eczema atopic 682
 eczematous contact dermatitis 483
 erythema multiforme 677
 lichen planus 681
 pityriasis rosea 680
 pruritus 615
 rabies 20
 Phenol poisoning 331
 Phenethylamine
 esterase 211 212
 guinea worm infection 217
 Phenurone 655 656 657 658
 Phenylhydrazine
 hemolytic anemia caused by 488
 polycythemia vera, 502 503
 Pheochromocytoma in cardiac decompen-
 sation 446
 Phlebectomy in regional ulcerative colitis 344
 Phlebotomy and thrombophlebitis
 40 379 380, 433, 472-477
 anesthetization of regional sympathetic
 ganglia 476
 bed rest 474 475
 cardiac decompression 438
 clot fragments prevention of transpor-
 tation of 476-477
 compression bandages 474
 dismal 475 477
 early ambulation 474
 hemorrhage 475
 heparin 473 477
 menadione bisulfite 476
 pneumonia 40
 polythene plastic tubing 475
 pneumonia 474-476
 protease hydrochloride, 476
 protein as sulfate 476
 pulmonary embolism 379 380, 433
 recurrent attacks prevention of 477
 resting position 474
 routinized therapy 476
 treatment, 474-477
 Phlebotomy fever 35
 Phlebotomy papules 35
 Phlebotomy
 (See Leukocytosis)
 Phosphates in hypoparathyroidism 274
 275
 Phosphoric acid 530
 Phosphorus radiography
 (See Radiophosphorus)
 Phrenic nerve operation in tuberculosis 3
 112 113 120 122 123 124
 Phthalylsulfathiazole
 (See Sulfathiazole)
 Physostigmine 644
 Picric acid
 alcoholism acute 601
 barb tartrate poisoning 605 606
 Fleischner 645
 headache 645
 intestinal hypotension 453
 peak anoxemia 652
 Pinta 147
 Pityriasis infections
 (See Enterobacter)
 Pityriasis
 diabetes insipidus 352
 diabetes 83
 menstruation 379
 Pityriasis extract
 barb tartrate poisoning 608
 headache 640
 scleroderma 471
 (See also Pityriasis)
 Pityriasis
 diabetes insipidus 351
 headache 630 638
 herpes zoster 11
 (See also Pityriasis extract)
 Pityriasis rosea 650
 Pityriasis rubra pilaris, 201
 Plague 99
 Plasmodium 132
 Plasmodium 143 149 154
 Pleurisy acute 384 385
 Pleurisy with effusion 126 125 385-386
 in scrophyl 385
 dyspnea 355 356
 empyema 386
 heparin 385
 penicillin 386
 phenobarbital 388
 pneumothorax 385 386
 procaïne 385
 syringic acid 385
 syringic acid 386
 thrombocytosis 385
 Pleurodynia infectious 197
 Plutonum 598 599
 Pneumococcal meningitis 34 57
 antipneumococcal rabbit serum 54
 focus of infection 56
 glucose 57
 hematuria 57
 intrathecal therapy 55 56
 molar sodium lactate 57
 mortality rates 54
 offspring 56
 penicillin 55 56 57
 prognosis, 57
 sodium bicarbonate 57
 sulfadiazine 55 56
 sulfamethoxazole 55 56
 sulfanilamide, 55
 sulfapyridine 54
 sulfathiazole 55 56 57
 transfusion 57
 Pneumococci 430
 Pneumococcal meningitis 381-383*
 antibiotics 381
 anticoagulation 381-382
 prevention 382
 tuberculosis 382
 Pneumocystis 115 124 131
 Pneumonia 39-47, 101 106 195 199
 200 437 438
 aerosol method in penicillin therapy 42
 allergic pulmonary reaction 41
 amino acids 44
 aminophylline 41
 anthrax 106
 antipneumococcal rabbit serum 46
 aspirin 46
 atropine sulfate 40
 autophagocytosis 41 43
 bacteriophage endocarditis 46
 bed rest, 45
 bronchial asthma 41
 bronchial obstruction 40
 carbon dioxide administration 40
 cardiac decompression 438
 chloromycetin 43
 codeine 46
 complications 46
 cough 46
 cultures of nose throat sputum 40
 dehydration 46
 diagnosis 39-40
 empyema 46
 endocarditis bacterial 46
 glucose 46
 iodides 41 45
 meteorism 46
 methylene blue 40 45-46
 papaverine hydrochloride 40
 penicillin 40, 41-42 45
 pericarditis, acute 431
 phenacetin 46
 phlebotomy 40
 pleural pain 46
 posttraumatic 40
 prevention 40-41
 pulmonary edema 41
 rheumatism 41
 scleritis 46
 scarlet fever and alexander serum 44
 sodium bicarbonate 44
 sodium chloride 46
 streptomycin 40 42 43 46
 sulfadiazine 46
 sulfamerazine 44
 sulfathiazole 46
 tetracycline 198 199 200
 tobacco 105
 vaccines 41
 Pneumoperitoneum 112 115 120 122
 123 126
 Pneumothorax extirpation 112 114
 internal 112
 Pneumothorax artificial 111 117 118
 114 115 122 123 124 125 126
 127 128 386
 spontaneous 385-389
 Poisoning by drugs and metals
 alcohol ethyl 600-602
 methanol 602-603
 arsenic 610-612
 arsine 612
 barb tartrate, 603 608
 bromine 605 609
 lead 614-616
 mercury 612 614
 Poliomyelitis acute 254
 Poliomyelitis acute 254
 acetylcholinergic acid 30
 artificial respiration 31
 atropine 30
 streptomycin 30
 hydrochloric acid 32
 detergent 30
 diet 27
 elimination 28
 epidemic, 30
 exercise 29-30
 gavage tube 27 28
 heart therapy 29
 hydrotherapy 29
 hypertension 29
 hypoxia 30
 isolation procedures 25-26
 Kenny pack 29
 laryngoscopy, 12
 medication 30
 mortality rates 30
 oxygen administration 31 33
 penicillin 30
 phlebotomy 30
 physiotherapy 28 30
 prevention 26
 prothymine 30
 psychologic measures 25-27
 respiratory difficulties 30-34
 serum 30
 suction of secretions from airway 11
 3
 vitamin 30
 bacteriophage 31 32
 vitamins, 27
 Polio extracts 369 370

- Pyridoxamine
angioneurotic edema 584
eczema, 682
erythema nodosum 196
hay fever 570
headache 647
pruritus ani 685
rhinitis allergica 574
serum sickness 537
urticaria 584
- Pyridoxine
(See Vitamin B₆)
- Pyrogenic bacterial 434-435
Pyromen 455
- Q fever 43 145 203
Quellung tests in influenza meningitis 52
Quinacrine
blackwater fever 155
malaria 131 232
Quincke's disease
(See Urticaria)
- Quintine
auricular fibrillation 407 408
auricular flutter 404
cardiac dysrhythmia 439 443
cardiac trauma 437
extrasystoles 404
heart block 403
myocardial infarction acute 419 421
paroxysmal auricular tachycardia 400
401
paroxysmal ventricular tachycardia 402
preexisting heart disease 434
rhythmic fever 69 70
sudden aural occlusion 468
surgical patient with heart disease 436
- Quinine
balantidiasis 194 195
blackwater fever 154 155
cerebral arteriosclerosis 654
glanders 103
malaria 130-131
multiple sclerosis 649
myasthenia gravis contra indicated in 565
parpura thrombocytopenic caused by 509
- Rabies III 23
antibiotics 25
hyperimmune serum 21 22
postvaccinal paralysis 20
preventive measures following injury by animal 19 20
Negri bodies 20
treatment of wounds 20
prevention in animals 19
vaccine 19 20 21 22
vitamin B complex 21
- Radonactive iodine 260 261 263 264
267 268
- Radophosphorus
anemia splenic 489
Hodgkin's disease 499 500
leukemia 491 494 497
multiple myeloma 510
polycythemia vera 502 504 505
- Rad ophthalmic 593 599
- Radium
actinomycosis 150
eye block 593
leukemia chronic granulocytic 494
relapsing fever 157
- Raynaud's disease 468-469
alcohol 469
anemia 468
climate 468
clothing warm 468
estrogens 469
menopause 469
menstruation 469
nitroglycerine ointment 469
sedation 468
sympatheticotomy 469
thyroid 469
tobacco 468
- Regional enteritis 352 354
amino acids 353
diet 353
granulomatous form localized 352 353
hyperplastic 353
ileocolostomy 352
prognosis 353 354
recurrent lesions 352 353
resection therapy 353
- Stenoforches 333
streptomycin 333
sulfasalazine 333
sulfathiazole 333
surgery 332
ulcerative colitis extensive 332 333
vitamins 333
- Regional enteritis 199
Regional ulcerative colitis 343-344
abscess perirectal 344
abscesses 343
arthritis 344
colocolostomy 343
colostomy 343
complicated 343-344
diarrhea 344
diet 343
enemas 343
erythema nodosum 344
hemorrhage 344
ileocolostomy 343
necrosis 344
perforation colonic 343
per rectal abscess 344
phlebitis 344
resection of diseased segment of bowel 343
streptomycin 343
structure of bowel 344
sulfasalazine 343
sulfathiazole 343
surgery 343
urinary tract infection of 344
- Re infection tuberculosis 120-121
Reiter's disease 197
Retaining foreign bodies paronychia 197
Retardant fever 155 159
arsenicals 156
aspirin 156
aztreomycin 157
benzoin salicylate 156
Berlitz 155
caffeine 156
codeine 156
diet 156
Herbimex phenomycin 156
ice packs 156
intravenous 156
louse borne type 155
morphine 156
neurophenazine 156
penicillin 156 157
potassium bismuth iodate 156
Sparacato 155 156
tick borne type 155
Renal calculi 314 331
Renal tuberculosis bilateral 129
unilateral 129
- Rheocin
acne 673
pustules 685
psoriasis 640
seborrheic dermatitis 678
linear crusts 674
- Reticulo-endothelial cytomycosis 135 136
Reticulum cell sarcoma
(See Hodgkin's disease)
- Reverberation in smallpox 13
Rheumatism fever 65 65 72 105 405
637 390
- ACTH 69 590
anionomyosis 68
aspirin 68 69
bed rest 69
blood-clotting agents 68
calcium benzoate succinate 68
corticosteroids 68
chemotherapy 71
colchicine 68
convalescence 71
enitamine 69
diet 61-68
diet 69
diuretics 70
erythema nodosum 293
fever therapy 70
local infection 70
heart block 603
heralds, 71
infection avoidance of 71
iron 70
mercurials, 70
suns and care, 67
oxyphen administration 69
penicillin 68 70
pericarditis acute 452
physiotherapy 71
prevention of epidemics 65
- Quinidine 69 70
ruminant therapy 70
salicylates 68 69
scarlet fever 63
streptococcal infection termination of 65-66 67
aspirin 67
convalescent serum 66
penicillin 65-66 67
sulfonamides 66
sulfonamides 66 III
antileukotony 70
vitamin 70
- Rheumatism palindromic 545 546
Rheumatoid arthritis
(See Arthritis rheumatoid)
- Rheumatoid synovitis
(See Arthritis rheumatoid)
- Rhinitis 575
Rhobavin
(See vitamin B₆)
- Rice diet
glomerulonephritis chronic 520
hypertensive vascular disease 451-453
- Rickets
(See Osteomalacia)
Rickettsia typhi 102
Rickettsia typhimurium 202
Rickettsial diseases 143 147 198 202
aztreomycin 145
aztreomycin 145
bed rest 145
Brill's disease 144
chloral hydrate 143
chloromycetin 145
codeine 146
diet 143
louse borne typhus epidemic 143 144
morphine 146
murine typhus fever 144
oliguria 145
para-aminobenzoic acid 146
paraldehyde 145
penicillin 146
prevention 143 145
Q fever 143
Rickettsialpox 144 145 198 202
Rocky Mountain spotted fever 144 145
scrub typhus, 143
sodium chloride 145
streptomycin 145
tetracycline 146
tetracycline disease 145 146
benzyl benzoate 145
dietary phthalate 145
organ administration 145
typhus fever 143 144
vaccines 143 144
- Rickettsialpox 144 145
Riedel's struma 271 272
- Ringer's solution
methyl alcohol poisoning 602
peritonitis 46
subacute bacterial endocarditis 426
thrombo-ulcerative colitis chronic 340
- Ringworm of the smooth skin 674
Rocky Mountain spotted fever 203
- Romney therapy
acne 673
actinomycosis 130 131
agranulocytosis 439
alimentary tuberculosis 334
amnesia 179
anemia splenic 439
anthrax 120
arthritis rheumatoid 636 641
asthma bronchial 532
blastomycosis 135
bronchiectasis 374
brucellosis chronic 374
cocci and cocci progressive 125
cryptococcosis 141
diphtheria III
edematous regional 333
erythromelalgia 470
exfoliative chronic hypertrophic 323
granuloma inguinale 163
heart block 403
herpes zoster 21
hemorrhage 593
Hodgkin's disease 499
hyperthyroidism 263 264
intoxication (see hydrocarbons) 550
leprosy 100
leukemia chronic granulocytic 492-494
chronic lymphocytic 497
lichen planus 688
lymphogranuloma venereum 35

- moniliasis 137
multiple myeloma 510
multiple sclerosis 648
myasthenia gravis 565
osteitis deformans 553
osteoarthritis 544
osteomyelitis, acute 364
phlebotomous 476
polycythemia vera 502 503 504
pruritus an. 683
psoriasis 680
regional enteritis 333
reticulo-endotheliosis leukemic chronic 493
rheumatoid fever 70
spondylitis 142
subarachnoid hemorrhage 635
temporal arteritis 459
thrombophlebitis 476
thyroiditis 272
tinea pedis 675
tuberculosis 120
- Roundworm infections**
(See Ascaris)
- Rubella 14
- Rus A
glomerulonephritis chronic 521
hypertensive vascular disease 453 454
preoperative preparation of jaundiced patient 359
- Salsaparyll 339**
Salsaparyll
arteriosclerosis obliterans 463
arteritis temporalis 458
arteritis rheumatoid 540
Bell's palsy 668
cocci diodermomycosis primary pulmonary 134
erythema nodosum 106
goat 552
headache 646
infectious pleurodynia 197
meningitis acute 432 433
pleurodynia infectious 197
Reiter's disease 197
rheumatic fever III 69
temporal arteritis 458
thromboangiitis obliterans 463
- Salicylic acid**
dermatitis herpeticiformis 678
moniliasis 137
pruritus an. 684
psoriasis 679 680
rheumatic fever prevention of 66
rheumatic dermatitis 678
thrombo-ulcerative colitis chronic 339
tinea cruris 674 675
tinea glabrous 674
tinea pedis 675
tinea versicolor 684
- Salicylism 68**
Salmonella choleraesuis 93
Salmonella enteritidis 93
Salmonella enteritidis
(See Salmonellosis)
Salmonella fever
(See Salmonellosis)
Salmonella paratyphi 89 92
Salmonella schottmulleri 93
Salmonella typhimurium 92
Salmonella typhosa 88 89 90 92
Salmonellosis 92 94 109
aureomycin 93
bismuth subcarbonate 93
carriers 93 94
chloromycetin III
diphtheria 93
diet 93
glucose 93
localized salmonella infections, 93
oxygen administration 93
paregoric 93
salmonella enteritidis 93
salmonella fever 92-93
salmonella infections localized 93
sulfaguanidine 93
sulfasuxid 93
tetracycline 93
transfusion whole blood III
vaccination 92
- Salpingitis in gonorrhea 74**
Salvarsan
multiple sclerosis 649
syphilis 164
Sanders oscillating bed 462 463 467 468
Sandy fever 35
Sanochrysin 538
- Sago virides 676
Scabies 676-677
Scarlet fever 63-65 66 67 200
antitoxin 64
arthritis 64
aspirin 64 67
bed rest 63 64
carditis 64
complications 63 64
convalescent serum III 66
desquamation 64
diet 64
glomerulonephritis 63
isolation of patients 63
mascotitis III 64
perniosis 64
stiff neck 63 III
penicillin 64 66 67
pooled convalescent serum 64
rheumatic fever 63
santonic 64
sodium bicarbonate 64
sore throat 64
sulfadiazine 64
tetracycline 200
treatment aim of 63
- Schaefer method of artificial respiration 595
Schick test 80 81 III 85
Schistosomiasis 205 207
anthelmintic 206 207
antimony compounds 206
cure 207
diarrhea 206
flood 206 207
hepatitis 207
sodium antimonyl tartrate 206
subpharynx 206 207
tatar emetic 206
- Schistosporynium crass 162**
Schwartz 471-472
acroscleroderma 471 472
acroscleritis 471
ACTH, 472
adrenal cortical hormone 472
androgen 472
anti-bismuth 472
Bismuth 472
circumscribed type 471
compound E 472
diffuse 471
dihydroxycholesterol 472
gold therapy 472
methyl chloride 472
nitrohydroxyacetate 472
pancreatic preparations 471
papaverine 472
physic therapy 471
proctostomy 471
prostaglandin 472
sclerodactylitis 471 472
sympathectomy 472
thyroid 471
vitamin E 472
- Scrub typhus 145
Scruvy, 297 298 307 308
Sea sickness 593
Seborrheic dermatitis 678 679
- Secoral**
arteriosclerosis obliterans 463
asthma bronchial 581
colon, lumenal disorders of 346
hay fever 570
influenza meningitis III
mumps 14
paroxysmal auricular tachycardia 401
polioencephalitis 50
postictic 57
tetanus 101
thromboangiitis obliterans 463
- Seisorm**
thromboangiitis obliterans 463
caused by 509
- Segmental ulcerative colitis**
(See Regional ulcerative colitis)
Septicemia 200, 201 202
Serologic tests for syphilis 366
Serum albumin
cerebral regulatory disturbances 632
type of hepatitis 525
nephrotic syndrome 516
uremia 522
Serum bilirubin in toxic hepatitis 350-351
Serum calcium in sprue syndrome 308
Serum sickness 584 588
accelerated reactions, 585
adrenalin chlorid 586
anaphylactic shock 585
anesthesia 587
- stomach reaction 585
hematolysis 587
calcium lotion 587
delayed reactions 585
desperated antitoxins 586 587
diphtheria toxin antitoxin 585
epinephrine 585 586 587 588
horse serum 584 585
prevent on 585 587
pyridoxamine 587
tetanus antitoxin 585
toxoid of diphtheria 587
tetanus 587
- Sigmoiditis enteritis**
(See Bacillary dysentery)
Shoulder-hand syndrome in acute myocardial infarction 422
Sickle cell anemia 483 484
Sincos 381-382
Silver nitrate
balanitis 195
cystitis 530
eczema nummular 683
eczematous contact dermatitis 683
laryngitis 365
pruritus an. 684
scorbic dermatitis 679
stomatitis herpetica 313
tinea pedis 675
tuberculosis 124
Silver nitrate poisoning 321
Silver salvarsan 648
Sistrionis disease 309
functional hypoglycemia 245
Sogulius
(See Hiccup)
- Sensuous**
bronchitis 372
bronchitis 372
scarlet fever 64
tetracycline 201 203
Spicy diet 398 317
Spiritus 592
Skid disease 672-684
Smellor 16 17
aqueous naphthalene chlorid 17
ascorbic acid 17
bathing 17
benic acid 17
diet 17
eye care 17
isolation of patient 16 17
penicillin 17
potassium permanganate 17
prevention 16
sulfathiazole 17
vaccine 17
varicoid 17
- Smallpox vaccine 17 19**
complications 18
revaccination 18
treatment of lesions 18
Smalwick operation 446 453
Smoking
(See Tobacco)
Snake bite 616-617
Sodium acetate, 522
Sodium acid phosphate 527
Sodium amylal
epilepsy 634
headache 630 639 643
hiccough 392
influenza meningitis 52
meningococcal meningitis 47
subarachnoid hemorrhage 636
tetanus 101
uremia 522
Sodium antimonyl tartrate
bute infections 205
schistosomiasis 206
Modium carbonate
anemia 522
anemia 522
arsenic poisoning 321
bacillary dysentery 95
cholera 97 98
gastrointestinal chronic recurrent superficial 312
glands 107
glomerulonephritis acute 513
lead poisoning 615
lower nephron nephrosis 526 527
melanosis 109
meningococcal meningitis 48
methyl alcohol poisoning 602 603
moniliasis, 138
peptic ulcer 326
pneumococcal meningitis 57
pyelitis 327

- tuberculosis 110f
 - alimentary 335
 - tuberculous meningitis 62
 - tularemia 77 78 79
 - typhoid fever 92
 - Streptococcus 134
 - Streptococcus (See Actinomyces)
 - Stroke
 - (See Cerebral circulatory disturbances)
 - Strophanthin
 - (See Ombin)
 - Stychnine
 - barbiturate poisoning 605
 - extrastyles 404
 - neutros 667
 - paroxysmal auricular tachycardia 401
 - Subacute bacterial endocarditis 424 431
 - anticoagulants 428
 - anticoagulant 424 427 428 429
 - benzoin 426
 - benzoic acid 426
 - carbamide 426
 - chloromycetin 424 427-428
 - complications 429
 - dexameth 428
 - diet 427
 - diodant 426
 - embolization 428 429
 - enterococci 424
 - etiologic organisms determination of 424
 - glucose 426
 - heparin 424 426 428
 - hyperkalemia 424
 - myocardial failure 429
 - para-aminobiphenyl acid 426
 - patent ductus arteriosus 429
 - penicillin 424 427
 - propylthiouracil 429
 - relapses 428-429
 - Ringer's solution 426
 - streptococci, alpha 424
 - beta hemolytic 424
 - gamma 424
 - nonhemolytic 424
 - streptomycin 424 427
 - sulfonamides 424
 - surgical patient 426
 - thrombophlebitis 428
 - transfusions 427
 - vitamins 427
- Subarachnoid hemorrhage 634-636
- acute massive 635
- angiography 635 636
- barbiturates, 636
- codeine sulfate 636
- dexameth 636
- diodant 635
- ligation of common carotid 635 636
- magnesium sulfate 636
- morphine 636
- paraldehyde 636
- roentgen therapy 635
- sodium amylal 636
- surgical puncture 635
- Sulby solution, 330
- Sulfanilic acid 330
- Sulfanilic acid (See Sulfanilic acid)
- Sulfonamide
 - (See Sulfanilic acid)
- Sulfonamide
 - barbiturate poison 605
 - cerebral circulatory disturbances 632
 - headache 639 644
- Sudden arterial occlusion 466-468
- alcohol 467 468
- diazepam 467
- dexameth 467 468
- embolism 467
- heart therapy 467
- heparin 467 468
- morphine sulfate 467
- oscillating bed 467 468
- papaverine hydrochloride 467 468
- quinidine 468
- Sanders oscillating bed 467 468
- spinal anesthesia 467
- temperature environmental 466 467
- tetraethyl ammonium chloride 467
- thrombectomy 468
- vitamin K 468
- Sulfasalazine
 - actinomycosis 130 131
 - agranulocytosis 489
 - anthrax 105 106
 - arthritis 549
 - brucellosis 76 77
 - chickenpox 16
- cholecystitis acute 361
- cholera 98
- cryptococcosis 141
- cystitis 529
- dysenteric bacillary 94 95 96
- erysipelas 81
- glands 107 108
- gonorrhea 73
- histoplasmosis 136
- influenza, 5
- influenza meningitis 51 52 53 54
- measles 13
- mellitus 108 109
- meningitis influenza 51 52 53 54
- pneumococcal 55 56
- streptococcal 58
- peritonitis 87
- plague 99
- pneumococcal meningitis 55 56
- scarlet fever, 64
- sterility male 784
- stomatitis 316
- streptococcal meningitis 51
- thyroid storm 265
- thyroiditis 271
- Vincent's angina 314
- Sulfasalazine
 - bacillary dysentery 95
 - cholera 98
 - salmonellosis 93
 - typhoid fever 92
- Sulfamerazine
 - agranulocytosis 489
 - cholecystitis acute 361
 - cystitis 529
 - meningococcal meningitis 47
 - pneumococcal meningitis 55 56
 - pneumonia 44
- Sulfanilic acid 108
- Sulfanilamide
 - agranulocytosis caused by 489
 - alimentary tuberculosis 335
 - chancroid infection 75
 - meningitis influenza 53
 - meningococcal 54
 - pneumococcal 54
 - streptococcal 51
 - peritonitis 87
 - tuberculosis alimentary 335
- Sulfapyridine
 - agranulocytosis caused by 489
 - alimentary tuberculosis 335
 - arthritis gonorrheal 74
 - dermatitis herpetiformis 677
 - meningitis influenza 53
 - meningococcal 47 50
 - pneumococcal 54
 - relapsing febrile nodular panniculitis 197
- Sulfasalazine
 - bacillary dysentery 95 96
 - cystitis 529
 - dysenteric 343
 - enteritis regional 333
 - gastro-intestinal complications of peritonitis, 85
 - regional ulcerative colitis 343
 - salmonellosis 93
 - typhoid fever 92
- Sulfasalazine
 - cystitis 529
 - enteritis regional 333
 - regional ulcerative colitis 343
 - thrombo-vascular colitis chronic 335
- Sulfasalazine
 - agranulocytosis caused by 489
 - anthrax 105 106
 - arthritis gonorrheal 74
 - chancroid infection 75
 - chickenpox 16
 - cholecystitis acute 361
 - colitis chronic thrombo-vascular 338
 - gonorrhea 73
 - lymphogranuloma venereum 36
 - mellitus 108
 - meningitis meningococcal 47
 - pneumococcal 51 52 53 54
 - staphylococcal 59
 - pneumonia 44
 - pyelitis 528
 - pyelonephritis 528
 - salmonella 17
 - stomatitis gangrenous 315
 - thrombo-vascular colitis chronic 338
 - typhoid fever 92
 - typhoid fever 92
 - typhoid fever 92
 - Vincent's angina 314
- Sulfasalazine
 - agranulocytosis caused by 489
 - anthrax 105 106
 - arthritis gonorrheal 74
 - chancroid infection 75
 - chickenpox 16
 - cholecystitis acute 361
 - colitis chronic thrombo-vascular 338
 - gonorrhea 73
 - lymphogranuloma venereum 36
 - mellitus 108
 - meningitis meningococcal 47
 - pneumococcal 51 52 53 54
 - staphylococcal 59
 - pneumonia 44
 - pyelitis 528
 - pyelonephritis 528
 - salmonella 17
 - stomatitis gangrenous 315
 - thrombo-vascular colitis chronic 338
 - typhoid fever 92
 - typhoid fever 92
 - typhoid fever 92
 - Vincent's angina 314
- Sulfasalazine
 - agranulocytosis caused by 489
 - anthrax 105 106
 - arthritis gonorrheal 74
 - chancroid infection 75
 - chickenpox 16
 - cholecystitis acute 361
 - colitis chronic thrombo-vascular 338
 - gonorrhea 73
 - lymphogranuloma venereum 36
 - mellitus 108
 - meningitis meningococcal 47
 - pneumococcal 51 52 53 54
 - staphylococcal 59
 - pneumonia 44
 - pyelitis 528
 - pyelonephritis 528
 - salmonella 17
 - stomatitis gangrenous 315
 - thrombo-vascular colitis chronic 338
 - typhoid fever 92
 - typhoid fever 92
 - typhoid fever 92
 - Vincent's angina 314
- Sulfasalazine
 - agranulocytosis caused by 489
 - anthrax 105 106
 - arthritis gonorrheal 74
 - chancroid infection 75
 - chickenpox 16
 - cholecystitis acute 361
 - colitis chronic thrombo-vascular 338
 - gonorrhea 73
 - lymphogranuloma venereum 36
 - mellitus 108
 - meningitis meningococcal 47
 - pneumococcal 51 52 53 54
 - staphylococcal 59
 - pneumonia 44
 - pyelitis 528
 - pyelonephritis 528
 - salmonella 17
 - stomatitis gangrenous 315
 - thrombo-vascular colitis chronic 338
 - typhoid fever 92
 - typhoid fever 92
 - typhoid fever 92
 - Vincent's angina 314
- Sulfasalazine
 - agranulocytosis caused by 489
 - anthrax 105 106
 - arthritis gonorrheal 74
 - chancroid infection 75
 - chickenpox 16
 - cholecystitis acute 361
 - colitis chronic thrombo-vascular 338
 - gonorrhea 73
 - lymphogranuloma venereum 36
 - mellitus 108
 - meningitis meningococcal 47
 - pneumococcal 51 52 53 54
 - staphylococcal 59
 - pneumonia 44
 - pyelitis 528
 - pyelonephritis 528
 - salmonella 17
 - stomatitis gangrenous 315
 - thrombo-vascular colitis chronic 338
 - typhoid fever 92
 - typhoid fever 92
 - typhoid fever 92
 - Vincent's angina 314
- Sulfasalazine
 - agranulocytosis caused by 489
 - anthrax 105 106
 - arthritis gonorrheal 74
 - chancroid infection 75
 - chickenpox 16
 - cholecystitis acute 361
 - colitis chronic thrombo-vascular 338
 - gonorrhea 73
 - lymphogranuloma venereum 36
 - mellitus 108
 - meningitis meningococcal 47
 - pneumococcal 51 52 53 54
 - staphylococcal 59
 - pneumonia 44
 - pyelitis 528
 - pyelonephritis 528
 - salmonella 17
 - stomatitis gangrenous 315
 - thrombo-vascular colitis chronic 338
 - typhoid fever 92
 - typhoid fever 92
 - typhoid fever 92
 - Vincent's angina 314
- Sulfasalazine
 - agranulocytosis caused by 489
 - anthrax 105 106
 - arthritis gonorrheal 74
 - chancroid infection 75
 - chickenpox 16
 - cholecystitis acute 361
 - colitis chronic thrombo-vascular 338
 - gonorrhea 73
 - lymphogranuloma venereum 36
 - mellitus 108
 - meningitis meningococcal 47
 - pneumococcal 51 52 53 54
 - staphylococcal 59
 - pneumonia 44
 - pyelitis 528
 - pyelonephritis 528
 - salmonella 17
 - stomatitis gangrenous 315
 - thrombo-vascular colitis chronic 338
 - typhoid fever 92
 - typhoid fever 92
 - typhoid fever 92
 - Vincent's angina 314
- Sulfasalazine
 - agranulocytosis caused by 489
 - anthrax 105 106
 - arthritis gonorrheal 74
 - chancroid infection 75
 - chickenpox 16
 - cholecystitis acute 361
 - colitis chronic thrombo-vascular 338
 - gonorrhea 73
 - lymphogranuloma venereum 36
 - mellitus 108
 - meningitis meningococcal 47
 - pneumococcal 51 52 53 54
 - staphylococcal 59
 - pneumonia 44
 - pyelitis 528
 - pyelonephritis 528
 - salmonella 17
 - stomatitis gangrenous 315
 - thrombo-vascular colitis chronic 338
 - typhoid fever 92
 - typhoid fever 92
 - typhoid fever 92
 - Vincent's angina 314
- Sulfasalazine
 - agranulocytosis caused by 489
 - anthrax 105 106
 - arthritis gonorrheal 74
 - chancroid infection 75
 - chickenpox 16
 - cholecystitis acute 361
 - colitis chronic thrombo-vascular 338
 - gonorrhea 73
 - lymphogranuloma venereum 36
 - mellitus 108
 - meningitis meningococcal 47
 - pneumococcal 51 52 53 54
 - staphylococcal 59
 - pneumonia 44
 - pyelitis 528
 - pyelonephritis 528
 - salmonella 17
 - stomatitis gangrenous 315
 - thrombo-vascular colitis chronic 338
 - typhoid fever 92
 - typhoid fever 92
 - typhoid fever 92
 - Vincent's angina 314
- Sulfasalazine
 - agranulocytosis caused by 489
 - anthrax 105 106
 - arthritis gonorrheal 74
 - chancroid infection 75
 - chickenpox 16
 - cholecystitis acute 361
 - colitis chronic thrombo-vascular 338
 - gonorrhea 73
 - lymphogranuloma venereum 36
 - mellitus 108
 - meningitis meningococcal 47
 - pneumococcal 51 52 53 54
 - staphylococcal 59
 - pneumonia 44
 - pyelitis 528
 - pyelonephritis 528
 - salmonella 17
 - stomatitis gangrenous 315
 - thrombo-vascular colitis chronic 338
 - typhoid fever 92
 - typhoid fever 92
 - typhoid fever 92
 - Vincent's angina 314
- Sulfasalazine
 - agranulocytosis caused by 489
 - anthrax 105 106
 - arthritis gonorrheal 74
 - chancroid infection 75
 - chickenpox 16
 - cholecystitis acute 361
 - colitis chronic thrombo-vascular 338
 - gonorrhea 73
 - lymphogranuloma venereum 36
 - mellitus 108
 - meningitis meningococcal 47
 - pneumococcal 51 52 53 54
 - staphylococcal 59
 - pneumonia 44
 - pyelitis 528
 - pyelonephritis 528
 - salmonella 17
 - stomatitis gangrenous 315
 - thrombo-vascular colitis chronic 338
 - typhoid fever 92
 - typhoid fever 92
 - typhoid fever 92
 - Vincent's angina 314
- Sulfasalazine
 - agranulocytosis caused by 489
 - anthrax 105 106
 - arthritis gonorrheal 74
 - chancroid infection 75
 - chickenpox 16
 - cholecystitis acute 361
 - colitis chronic thrombo-vascular 338
 - gonorrhea 73
 - lymphogranuloma venereum 36
 - mellitus 108
 - meningitis meningococcal 47
 - pneumococcal 51 52 53 54
 - staphylococcal 59
 - pneumonia 44
 - pyelitis 528
 - pyelonephritis 528
 - salmonella 17
 - stomatitis gangrenous 315
 - thrombo-vascular colitis chronic 338
 - typhoid fever 92
 - typhoid fever 92
 - typhoid fever 92
 - Vincent's angina 314
- Sulfasalazine
 - agranulocytosis caused by 489
 - anthrax 105 106
 - arthritis gonorrheal 74
 - chancroid infection 75
 - chickenpox 16
 - cholecystitis acute 361
 - colitis chronic thrombo-vascular 338
 - gonorrhea 73
 - lymphogranuloma venereum 36
 - mellitus 108
 - meningitis meningococcal 47
 - pneumococcal 51 52 53 54
 - staphylococcal 59
 - pneumonia 44
 - pyelitis 528
 - pyelonephritis 528
 - salmonella 17
 - stomatitis gangrenous 315
 - thrombo-vascular colitis chronic 338
 - typhoid fever 92
 - typhoid fever 92
 - typhoid fever 92
 - Vincent's angina 314
- Sulfasalazine
 - agranulocytosis caused by 489
 - anthrax 105 106
 - arthritis gonorrheal 74
 - chancroid infection 75
 - chickenpox 16
 - cholecystitis acute 361
 - colitis chronic thrombo-vascular 338
 - gonorrhea 73
 - lymphogranuloma venereum 36
 - mellitus 108
 - meningitis meningococcal 47
 - pneumococcal 51 52 53 54
 - staphylococcal 59
 - pneumonia 44
 - pyelitis 528
 - pyelonephritis 528
 - salmonella 17
 - stomatitis gangrenous 315
 - thrombo-vascular colitis chronic 338
 - typhoid fever 92
 - typhoid fever 92
 - typhoid fever 92
 - Vincent's angina 314
- Sulfasalazine
 - agranulocytosis caused by 489
 - anthrax 105 106
 - arthritis gonorrheal 74
 - chancroid infection 75
 - chickenpox 16
 - cholecystitis acute 361
 - colitis chronic thrombo-vascular 338
 - gonorrhea 73
 - lymphogranuloma venereum 36
 - mellitus 108
 - meningitis meningococcal 47
 - pneumococcal 51 52 53 54
 - staphylococcal 59
 - pneumonia 44
 - pyelitis 528
 - pyelonephritis 528
 - salmonella 17
 - stomatitis gangrenous 315
 - thrombo-vascular colitis chronic 338
 - typhoid fever 92
 - typhoid fever 92
 - typhoid fever 92
 - Vincent's angina 314
- Sulfasalazine
 - agranulocytosis caused by 489
 - anthrax 105 106
 - arthritis gonorrheal 74
 - chancroid infection 75
 - chickenpox 16
 - cholecystitis acute 361
 - colitis chronic thrombo-vascular 338
 - gonorrhea 73
 - lymphogranuloma venereum 36
 - mellitus 108
 - meningitis meningococcal 47
 - pneumococcal 51 52 53 54
 - staphylococcal 59
 - pneumonia 44
 - pyelitis 528
 - pyelonephritis 528
 - salmonella 17
 - stomatitis gangrenous 315
 - thrombo-vascular colitis chronic 338
 - typhoid fever 92
 - typhoid fever 92
 - typhoid fever 92
 - Vincent's angina 314
- Sulfasalazine
 - agranulocytosis caused by 489
 - anthrax 105 106
 - arthritis gonorrheal 74
 - chancroid infection 75
 - chickenpox 16
 - cholecystitis acute 361
 - colitis chronic thrombo-vascular 338
 - gonorrhea 73
 - lymphogranuloma venereum 36
 - mellitus 108
 - meningitis meningococcal 47
 - pneumococcal 51 52 53 54
 - staphylococcal 59
 - pneumonia 44
 - pyelitis 528
 - pyelonephritis 528
 - salmonella 17
 - stomatitis gangrenous 315
 - thrombo-vascular colitis chronic 338
 - typhoid fever 92
 - typhoid fever 92
 - typhoid fever 92
 - Vincent's angina 314
- Sulfasalazine
 - agranulocytosis caused by 489
 - anthrax 105 106
 - arthritis gonorrheal 74
 - chancroid infection 75
 - chickenpox 16
 - cholecystitis acute 361
 - colitis chronic thrombo-vascular 338
 - gonorrhea 73
 - lymphogranuloma venereum 36
 - mellitus 108
 - meningitis meningococcal 47
 - pneumococcal 51 52 53 54
 - staphylococcal 59
 - pneumonia 44
 - pyelitis 528
 - pyelonephritis 528
 - salmonella 17
 - stomatitis gangrenous 315
 - thrombo-vascular colitis chronic 338
 - typhoid fever 92
 - typhoid fever 92
 - typhoid fever 92
 - Vincent's angina 314
- Sulfasalazine
 - agranulocytosis caused by 489
 - anthrax 105 106
 - arthritis gonorrheal 74
 - chancroid infection 75
 - chickenpox 16
 - cholecystitis acute 361
 - colitis chronic thrombo-vascular 338
 - gonorrhea 73
 - lymphogranuloma venereum 36
 - mellitus 108
 - meningitis meningococcal 47
 - pneumococcal 51 52 53 54
 - staphylococcal 59
 - pneumonia 44
 - pyelitis 528
 - pyelonephritis 528
 - salmonella 17
 - stomatitis gangrenous 315
 - thrombo-vascular colitis chronic 338
 - typhoid fever 92
 - typhoid fever 92
 - typhoid fever 92
 - Vincent's angina 314
- Sulfasalazine
 - agranulocytosis caused by 489
 - anthrax 105 106
 - arthritis gonorrheal 74
 - chancroid infection 75
 - chickenpox 16
 - cholecystitis acute 361
 - colitis chronic thrombo-vascular 338
 - gonorrhea 73
 - lymphogranuloma venereum 36
 - mellitus 108
 - meningitis meningococcal 47
 - pneumococcal 51 52 53 54
 - staphylococcal 59
 - pneumonia 44
 - pyelitis 528
 - pyelonephritis 528
 - salmonella 17
 - stomatitis gangrenous 315
 - thrombo-vascular colitis chronic 338
 - typhoid fever 92
 - typhoid fever 92
 - typhoid fever 92
 - Vincent's angina 314
- Sulfasalazine
 - agranulocytosis caused by 489
 - anthrax 105 106
 - arthritis gonorrheal 74
 - chancroid infection 75
 - chickenpox 16
 - cholecystitis acute 361
 - colitis chronic thrombo-vascular 338
 - gonorrhea 73
 - lymphogranuloma venereum 36
 - mellitus 108
 - meningitis meningococcal 47
 - pneumococcal 51 52 53 54
 - staphylococcal 59
 - pneumonia 44
 - pyelitis 528
 - pyelonephritis 528
 - salmonella 17
 - stomatitis gangrenous 315
 - thrombo-vascular colitis chronic 338
 - typhoid fever 92
 - typhoid fever 92
 - typhoid fever 92
 - Vincent's angina 314
- Sulfasalazine
 - agranulocytosis caused by 489
 - anthrax 105 106
 - arthritis gonorrheal 74
 - chancroid infection 75
 - chickenpox 16
 - cholecystitis acute 361
 - colitis chronic thrombo-vascular 338
 - gonorrhea 73
 - lymphogranuloma venereum 36
 - mellitus 108
 - meningitis meningococcal 47
 - pneumococcal 51 52 53 54
 - staphylococcal 59
 - pneumonia 44
 - pyelitis 528
 - pyelonephritis 528
 - salmonella 17
 - stomatitis gangrenous 315
 - thrombo-vascular colitis chronic 338
 - typhoid fever 92
 - typhoid fever 92
 - typhoid fever 92
 - Vincent's angina 314
- Sulfasalazine
 - agranulocytosis caused by 489
 - anthrax 105 106
 - arthritis gonorrheal 74
 - chancroid infection 75
 - chickenpox 16
 - cholecystitis acute 361
 - colitis chronic thrombo-vascular 338
 - gonorrhea 73
 - lymphogranuloma venereum 36
 - mellitus 108
 - meningitis meningococcal 47
 - pneumococcal 51 52 53 54
 - staphylococcal 59
 - pneumonia 44
 - pyelitis 528
 - pyelonephritis 528
 - salmonella 17
 - stomatitis gangrenous 315
 - thrombo-vascular colitis chronic 338
 - typhoid fever 92
 - typhoid fever 92
 - typhoid fever 92
 - Vincent's angina 314
- Sulfasalazine
 - agranulocytosis caused by 489
 - anthrax 105 106
 - arthritis gonorrheal 74
 - chancroid infection 75
 - chickenpox 16
 - cholecystitis acute 361
 - colitis chronic thrombo-vascular 338
 - gonorrhea 73
 - lymphogranuloma venereum 36
 - mellitus 108
 - meningitis meningococcal 47
 - pneumococcal 51 52 53 54
 - staphylococcal 59
 - pneumonia 44
 - pyelitis 528
 - pyelonephritis 528
 - salmonella 17
 - stomatitis gangrenous 315
 - thrombo-vascular colitis chronic 338
 - typhoid fever 92
 - typhoid fever 92
 - typhoid fever 92
 - Vincent's angina 314
- Sulfasalazine
 - agranulocytosis caused by 489
 - anthrax 105 106
 - arthritis gonorrheal 74
 - chancroid infection 75
 - chickenpox 16
 - cholecystitis acute 361
 - colitis chronic thrombo-vascular 338
 - gonorrhea 73
 - lymphogranuloma venereum 36
 - mellitus 108
 - meningitis meningococcal 47
 - pneumococcal 51 52 53 54
 - staphylococcal 59
 - pneumonia 44
 - pyelitis 528
 - pyelonephritis 528
 - salmonella 17
 - stomatitis gangrenous 315
 - thrombo-vascular colitis chronic 338
 - typhoid fever 92
 - typhoid fever 92
 - typhoid fever 92
 - Vincent's angina 314
- Sulfasalazine
 - agranulocytosis caused by 489
 - anthrax 105 106
 - arthritis gonorrheal 74
 - chancroid infection 75
 - chickenpox 16

- tuberculosis 110f
 alimentary 335
 tuberculous meningitis 60-62
 tularemia 77 78 79
 typhoid fever 92
 Streptothricin n, 134
 Streptothricin
 (See Actinomycosis)
 Suck
 (See Cerebral circulatory disturbances)
 Suckling
 (See Unbain)
 Strychnine
 labotrate poisoning 605
 extrasystoles 404
 neuritis 667
 paronychia acicular tachycardia 403
 Subacute bacterial endocarditis 424 431
 anticoagulants 428
 aureomycin 424 427 428 429
 benedict 424
 benzoic acid 424
 caronam d 424
 chloromycetin 424 427-428
 complications 429
 dicumaryl 428
 diet 427
 diodrat 426
 embolism 428 429
 enterococci 424
 etiologic organisms determination of 424
 glucose 426
 heparin 424 426 428
 hyperkalemia 424
 myocardial failure 429
 para-am. obipipruric acid 426
 patent ductus arteriosus 429
 penicillin 424 427
 prophylaxis 429
 relapses 428-429
 Ringer's solution 426
 streptococci alpha 424
 beta hemolytic 424
 gamma 424
 gonhemolytic 424
 streptomycin 424 427
 sulfacetamides 424 427
 au gual patient 426
 thrombophlebitis 428
 transfusions 427
 vitamins 427
 Subarachnoid hemorrhage 634-636
 acute massive 635
 arteriography 635 636
 barbiturates, 636
 code ne sulfate 636
 dexameth 636
 dexameth 636
 ligation of common carotid 635 636
 magnesium sulfate 636
 morphine 636
 paraldehyde 636
 rocuron therapy 635
 sodium amylal 636
 spinal puncture 635
 Sully's solution, 330
 Sulfanilic acid
 (See Sulfanilamide)
 Sulfone
 barb tartrate poison 606
 cerebral circulatory disturbances 632
 headache 639 644
 Sudden arterial occlusion 466 468
 alcohol 467 468
 d'athery 467
 dicumaryl 467 468
 embolism 468
 heat therapy 467
 heparin 467 468
 morphine sulfate 467
 oscillating bed 467 468
 papaverine hydrochloride 467 468
 quindine 468
 Saunders oscillating bed 467 468
 spinal anesthesia 467
 temperature environmental 466 467 468
 tetra-ethyl-ammonium chloride 467
 thrombectomy 468
 vitamin K 468
 Sulfadiazine
 actinomycosis, 130 131
 agranulocytosis 459
 anthrax 105 106
 arthritis 549
 brucellosis 76 77
 chiknspox 16
 cholecystitis acute 361
 cholera 98
 cryptococcosis 141
 cystitis 529
 dysentery bacillary 94 95 96
 erysipelas 72
 glands 107 108
 gonorrhea 73
 histoplasmosis 136
 influenza 5
 influenza menigitis 81 82 53 54
 measles 13
 melioidosis 108 109
 meningitis influenza 81 52 53 54
 pneumococcal 88 56
 streptococcal 58
 pertussis 87
 plague 99
 pneumococcal meningitis 88 56
 scarlet fever, 64
 sterility male 754
 stonolitis 316
 streptococcal meningitis 58
 thyroid storm 265
 typhoid fever 92
 Vincent's angina 314
 Sulfaguanidine
 bacillary dysentery 93
 cholera 98
 salmonellosis 93
 typhoid fever 92
 Sulfamerazine
 agranulocytosis 489
 cholelithiasis acute 361
 cystitis 529
 meningococcal meningitis 47
 pneumococcal meningitis 55 56
 pneumonia 44
 Sulfamethazine 108
 Sulfanilamide
 agranulocytosis caused by 459
 alimentary tuberculosis, 335
 chancroid infection 75
 meningitis influenza 53
 meningococcal 47 50
 pneumococcal 54
 streptococcal 58
 peritonsillar abscess 488
 tuberculosis alimentary 335
 Sulfapyridine
 agranulocytosis caused by 489
 alimentary tuberculosis 335
 arthritis gonorrheal 34
 dermatitis herpetiformis 677
 meningitis influenza 53
 meningococcal 47 50
 pneumococcal 54
 relapsing febrile nodular panniculitis 197
 Sulfasuxidone
 bacillary dysentery 95 96
 cystitis 529
 diverticulitis 348
 enteritis regional 333
 gastro-intestinal complications of peritonsillar abscess 88
 regional ulcerative colitis 343
 salmonellosis 93
 typhoid fever 92
 Sulfathiazole
 cystitis 529
 enteritis regional 333
 regional ulcerative colitis 343
 thrombo-ulcerative colitis chronic 338 339
 Sulfathiazole
 agranulocytosis caused by 489
 anthrax 105 106
 arthritis gonorrheal 74
 chancroid infection 75
 chiknspox 16
 cholelithiasis acute 361
 colitis chronic thrombo-ulcerative 338 339
 gonorrhea 73
 lymphogranuloma venereum 36
 melioidosis 108
 meningitis meningococcal 55 56 57
 pneumococcal 55 56 57
 staphylococcal 59
 pneumonia 44
 pyelitis 528
 pyelonephritis 528
 scurvy 165
 stomatitis gangrenous 315
 thrombo-ulcerative colitis chronic 338 339
 thrombophlebitis 157
 Vincent's angina 314
 Sulfur
 acne 673
 dermatitis herpetiformis 678
 monilia 137
 pruritus ani 684
 scabies 675
 scorbatic dermatitis 678 679
 tinea cruris 674 675
 tinea glabrous 674
 Sunstroke 592
 Suppositories glycerol 346
 Suram
 onchocerciasis 216
 trypanosomiasis African 161
 Surgical patient with heart disease
 (See Heart disease in the surgical patient)
 Swamp fever 147
 Swimmer's itch 207
 Swine sickness 593
 Sympathetic
 acrocyanosis 470
 arteriosclerosis obliterans 463
 cerebral hemorrhage 628
 headache 641
 livedo reticularis 470
 multiple sclerosis 649
 Raynaud's disease 469
 scleroderma 472
 shoulder-hand syndrome 422
 thrombophlebitis obliterans 462
 Sympathomimetic drugs
 atelectasis 378
 bronchospasm 371
 bronchitis chronic 371
 emphysema 375
 Syphilis, 306
 Syphilis 306
 Sympyromy 350
 Syphilis 163 186 202 324 390 405 409
 acquired immunity 164
 aortic stenosis 168 170
 arsenic 168 169
 aureomycin 186
 benign late gummatous 171 173
 follow up therapeutic program 172
 bismuth 168 169 170 171
 cardiovascular 173 174
 bad test 173
 bismuth 173
 d'athery 173
 diuretics 173
 fluoroscopy, 174
 follow up therapeutic program 174
 penicillin 174
 treatment failure 174 176
 chancre immaturity 163
 congenital
 (See Syphilis infantile congenital and late congenital)
 control 186
 coronary insufficiency 409
 cross immunity 163 166
 dermatophytosis 168
 early 168 170
 flocculation tests 163 166
 gummatous 171 173
 heart block 403
 history, 163 164
 immunity 164 166
 infantile congenital 176 178
 follow up therapeutic program 177
 Jarisch Herxheimer reaction 178
 penicillin 177 178
 re-treatment 178
 treatment failure 178
 late congenital 178 179
 follow up therapeutic program 178
 Jarisch Herxheimer reaction 179
 penicillin 178 179
 re-treatment 179
 treatment failure 179
 late latent 170 171
 follow up therapeutic program 170 171
 macular, 169 170
 mediastinal abscess 390
 natural immunity 164
 neurosyphilis 182 185
 asymptomatic 184 185
 epilepsy 185
 Erb's spinal spasm paraplegia 185
 follow up therapeutic program 183
 hyperpyrexia 182 185
 Jarisch Herxheimer reaction 185
 meningitis acute 184 185
 meningovascular 184 185
 nerve deafness 185
 paresis, 182 183 184 185

Syphilis—(continued)

- penicillin 152 183 184 185
re-treatment 185
spinal fluid examination 182
syndromes 182
tabes dorsalis 182 183 184
taboparalysis 182 183 185
treatment failure 185
ocular 179 182
 interstitial keratitis 180-181
 follow-up therapeutic program 180
 hyperpyrexia 180-181
 Jarisch-Herxheimer reaction 181
 penicillin 180
 symptoms 180
 testament failure 180 181
 uritis 179 180
 Jarisch-Herxheimer reaction 180
 penicillin 179 180
 treatment failure 179 180
 primary optic atrophy 181 182
 hyperpyrexia 181 182
 Jarisch-Herxheimer reaction 181
 penicillin 181 182
 re-treatment 181 182
 treatment failure 181
 oral penicillin treatment 181
 ostomyelitis 172
 oropharyngeal hydrochloride 166
 penicillin 164
 ping-pong 165
 potassium iodide 164
 pregnancy 173 176
 arsenic, 176
 bismuth 176
 infants follow-up examination of 175
 follow-up therapeutic program 175
 penicillin 173 176
 re-infection on 176
 re-treatment 176
 serologic tests 173
 therapeutic shock 176
 prevent on 184
 re-infection 185 169
 relapse 169
 salvarsan 164
 serologic tests 165
 spinal fluid examination 163
 atomach involvement 124
 tetramycin 202
 therapeutic paradox 171 173 174
 Treponema pallidum 164 163 166
 vascular 172 173
 urticaria 168
 Tobes dorsalis 182 183 184 185
 Tachycardia paroxysmal auricular 400-401
 paroxysmal ventricular 401-402 421
 419
 cardiac decompensation 439
 Taenia saginata 207 208
 Taenia solium 103 109
 Tannic acid poison 321
 Tapeworm infections 207 209
 alabrum 208
 carbon tetrachloride 208
 Diphyllobothrium latum 207 104
 Dipylidum caninum 207
 Echinococcus granulosus 208 109
 Heterostephanus 208
 Hymenolepis nana 207
 intestinal 208
 larval 209
 magnesium sulfate 208
 obscure 208
 prevention 209
 Taenia saginata 207 208
 Taenia solium 209 209
 tetrachloride 208
 tetrachloroethylene 208
 Tartar emetic
 granuloma inguinale 167
 leishmaniasis 155 159 160
 schistosomiasis 208
 Tartar emetic poisoning 322
 Temporal arteritis 438-439
 potassium iodide 439
 roentgen therapy 439
 salicylates 438
 Temporomandibular joint disease of 445
 Terp n hydrate 324
 Teramycin 198-204
 schistosomiasis 203
 administered on 199-200
 Aerobacter aerogenes 202
 anemia 199 203
 asthma 199 202

- bacteroides bacteremia 202
brucellosis 203
brucellosis acute 203
brucellosis acute 198 199 201
cellulitis 200 201
conjunctivitis 201
dosage 199 200
erysipelas 201
erysipelas 199 200
Escherichia coli 202
Fusillidex 203
fusillidex 203
gonorrhea 201
granuloma inguinale 202
hemophilus infection 202
Hemophilus influenzae 202
Hemophilus pertussis 202
herpes zoster 202 203
ileitis vaginal 199
impetigo 201
influenza 202 203
laryngotracheitis 203
lymphogranuloma venereum 202 203
meningitis meningococcal 202
otitis media bilateral 200 201 203
paratyphoid 199
peritonitis 200 203
pertussis 202 201
pharyngitis streptococcal 199 200 201
pneumococcal pneumonia 199 200
pneumonia 198 199
primary atypical pneumonia 200
Proctosiphon 202
pyelonephritis 201 202
Q fever 203
regional ileitis 199
Rickettsia prowazekii 202
Rickettsia typhus 202
rickettsial diseases 146 198 202
rickettsialpox 202
Rocky Mountain spotted fever 203
scarlet fever 200
septicemia 200 201 202
sinusitis 202 203
staphylococcal infections 201
Staphylococcus aureus 202
streptococcal infections 200-201
streptococcal pharyngitis 199 200
Streptomyces rimosus 198
syphilis 202
terramycin penicillinase gram-negative or
 anemia 202
tonsillitis acute follicular 200
toxicity 198
tracheobronchitis 203
ulceration 202
typhoid fever 199 203
typhus 194 202
urinary tract infections 198 199 200
 201 202
 Testicular disease 253 267
 Testosterone propionate
 Addison's disease 258
 coronary insufficiency 412
 hemochromatosis 243
 hypoparathyroidism 350 356
 impotence 284
 menorrhagia 259
 metrorrhagia 259
 Tetanus 102 104
 asthenia 102 103
 atrophy 103
 avertin 101
 catheterization of bladder 102
 curare 102
 cyanosis 102
 dysentery hydrochloride 101
 dysentery 102
 epinephrine hydrochloride 103
 glucose 102
 immunization 103 104
 magnesium sulfate 101
 morphine 101
 pneumonia 103
 prophylaxis 103 104
 roentgen examination of spine 103
 several 101
 sedation 103
 sedation amylal 101
 sedation chloral 102
 spasms, control of 101 103
 surgical procedures 103
 toxoids 104
 vaccines 104
 Tetanus antitoxin in serum sickness 355
 Tetanus toxoid 65 81 82 84
 Tetany in hypoparathyroidism 273 274
 275

Tetrachloride

- (See Carbon tetrachloride)
Tetrachloroethylene
 anesthetics 213
 anesthetics 210
 tapeworm infections 208
 Tetraethylammonium chloride
 arteriosclerosis obliterans 462
 sudden arterial occlusion 461
 thromboangiitis obliterans 462
 Thiamine chloride
 (See Vitamin B₁)
 Thalassemia 438 434
 Theobromine
 anemia petrous 412
 cardiac decompensation 440
 coronary insufficiency 412
 glomerulonephritis 312 315
 (See also Theocaine)
 Theocaine
 anterior fibulation 403
 cerebral arteriosclerosis 434
 heart block 405
 Theophylline ointment
 excess atopy 352
 pruritus 405
 Theophylline ethylenediamine
 (See Aminophylline)
 Thermal states 501 505
 Therapeutic fever 392
 Thrombosis
 cardiac decompensation 439
 septicemic syndrome 517
 Thrombosis
 aggravation caused by 489
 anemia petrous 412
 cardiac decompensation 439
 coronary insufficiency 412
 hyperthyroidism 201 202 204 205
 206
 thyroiditis 211
 Thrombocytosis 355 433
 Thrombocytosis 111, 112 114 112 113
 124 125 133
 Three-day fever 315
 Thrombotomy in sudden arterial occlusion 463
 Thrombotomy 450-466
 Thrombotomy
 anemia 451 452
 leukemic reticuloendotheliosis chronic
 495
 preoperative preparation of jaundiced
 patient 339
 Thromboplastin in tuberculosis 128
 Thrombophlebitis
 (See Phlebotomy)
 Thrombotic drugs 456
 Thrombotic arterial 438
 Thrombotic ulceration of the chronic 316
 341
 acids 340
 ACTH 339
 alkalosis 340
 anemia 339
 aspirin 339
 bed rest 338
 calcium chloride 340
 cold water 337
 colostomy 341
 cystitis 340
 dehydration 340
 diuretics 337 340
 diuretics 336 341
 diet 337-338
 ergosterol irradiated 337
 Estulin per anal 340 341
 fecal infection removal of 340
 Hartman's solution 340
 hemorrhage 340
 hypoproteinemia 339
 sclerotomy 341 342
 sodium, mixture of 338
 urination intestinal 340
 rhizogen 338
 magnesium chloride 340
 mental attitude of patient 337 338
 neoplasms 341
 nursing care 338
 oxygen 338 340
 oxytocin administration 339
 pallidus 340
 parenteral administration of fluids 340
 penicillin 339
 perforation 342
 peritoneal fistulas 340 341
 phthalic acid 338 339
 polymer 341
 potassium chloride 340

- prognosis 341-342
relapse 342
Ringer's solution 340
salicylism 339
salicyl c acid, 339
sodium bicarbonate 340
sodium chloride 337-340
sodium lactate 340
stomach 340-341
structures 341
sulfathiazole 339-340
sulfathiazole 338-339
symptoms 336
surgery 340-341
transfusion of whole blood 339
vaccine 338
vagotomy 341
vitamin B 337-338
wheat germ 337
- Thrush intra oral 137-138
Thymectomy, 564-565
Thymol
actinomycosis 130-137
actinomycosis 213
coccidioidomycosis progressive 135
herpes zoster 10
neuritis 666
Thyrocardiac disease 266-267
Thyroid extract
amenorrhea 277
arteriosclerosis obliterans 461
brucellosis 77
headache 640
hypothyroidism 269-270
myasthenia gravis contraindicated in 363
nephrotic syndrome 518
obesity 247
Raynaud's disease, 469
rheumatic allergy 573
scleroderma 471
thrombophlebitis obliterans 461
Thyroidectomy
angina pectoris 412
cardiac decompensation 445
coronary insufficiency 412
hyperthyroidism 260-261-262-263-264-265-266
surgical patient with heart disease 436
Thyroiditis 271-272
acute 271
amyloidosis of thyroid 271
antithyroid 271
aspirin 271
chronic 271-272
coccidia 271
granuloma infectious 271
Hashimoto's struma 271
iodine packs 271
lobectomy 271
leukemia 272
myxedema 272
penicillin 271
Riedel's struma 271-272
roentgen therapy 272
streptomycin 271
sulfadiazine 271
surgery 272
thiouracil 271
thyroid administration 272
tuberculous 271-272
Thyrotropic hormone 309
Tick fever
(See Relapsing fever)
Tinea cruris, 674-675
Tinea glabris 674
Tinea manus 676
Tinea pedis 675-676
Tinea versicolor 673-674
Tinnitus in Ménière's syndrome 669-670
671
Tubercu-
angina pectoris 410
arteriosclerosis obliterans 460
cerebral circulatory disturbances 629
coronary insufficiency 410
glomerulonephritis chronic 519
liverectulitis 470
myocardial infarction acute 474-475
Raynaud's disease 468
scleroderma 471
thrombophlebitis obliterans 460
Tubercu-
603
Toluene blue
anemia hypoplastic 491
chronic radicular injuries 508
purpura idiopathic thrombocytopenic 508
Tonillectomy in rheumatic fever 70
- Tonsillitis 200-201
Toward 584
Tordella 141
Tox c hepatis
(See Hepatitis toxic)
Toxicity of streptomycin
tuberculosis meningitis 62
tuberculosis 79
Toxicity of sulfonamides
influenza meningitis 54
meningococcal meningitis 50
Toxoplasmosis
chorioamnionitis 157
sulfathiazole 157
typhoid vaccine 158
Typhoeulitis acute 203-206-207
acetylsalicylic acid 369
serosal therapy 370
antibiotics 369
barbiturates, 369
bed rest 369
benzoin 369
bromides 369
chloroform 369
codeine 369-370
cough 369-370
expectorants 369
nasal congestion 369
oxygen 369
pruritus hydrochloride 369
steam inhalation 369
terramycin 203
troches 370
Tracheotomy
diphtheria, laryngeal 84
hypoparathyroidism 274
influenza meningitis 51
polymyelitis acute 31-32
Trench sickness 593
Trench mouth 314
Trepanol 335
Treponema carotum 187
Treponema pallidum 164-165-166-168-169
Treponema pertenue 186-188
Tribromethanol
(See Avertin)
Trichocyst 212
Trichomonas hominis 193
Trichomonas 195
Trichophyton moniliforme 139
Trichophyton gypseum 675
Trichophyton purpurum 675
Trichophyton 461
Tridone
epilepsy 655-656-657
parkinsonism 653
Tropical treponematoses 186-187
Jarisch-Herxheimer reaction 187
penicillin 187
re-treatment 187
treatment failure 187
Treponema pertenue 186
Trypanellene 7
Trypanosomiasis
(See Leishmaniasis)
Trypanosomiasis African 161
Trypanosomiasis South American 161-162
Bayer 7602 161
myocarditis 162
Schistosomum 162
Trypanosoma 161
Tsetse fly 162
Tuberculosis 122
Tuberculosis 109-128
alimentary
(See Alimentary tuberculosis)
amenorrhea 277
antibiotic 114
apical cavities large 123
bed rest 110-111
bilateral bronchogenic 123
bilateral renal 129
bronchial 123-124
bronchogenic c 120-121-123
cavernous 115-123
cavities apical 123
cavities in lower portions 123
chronic hematogenous type 119-120
collapse therapy 110-111-115-119-120-123-125-127-128
diabetes 128-129
dihydrostreptomycin 117
early infiltrates 121-122
erythema nodosum 195
excise re-grafted 127
genito-urinary 128-130
hematogenous 119-120
hemorrhage 127-128
- Wilar region, 120-125
infravascular cavity early with bronchopneumonia 122
lobectomy 115-117-124
miliary 118-119
Mond's drainage 112-114-115-123
obesity 249
paralysis of diaphragm artificial 117
Parrot's law 120
patient dealing with 125-127
pericarditis acute 432
phrenic nerve operations 112-113-120-122-123-126
pleurisy complicating pneumothorax 113
pleurisy with effusion 124-125
pneumococcal 115
pneumocystis extrapleural 112-114-119
pneumomycosis internal 112
pneumoperitoneum 112-113-120-122-123-126
pneumothorax artificial 111-112-113-114-119-127-123-124-125-128
pregnancy 128
primary infection progressive 120
rehabilitation of patient 127
reinfection 120-123
resection 115
roentgen therapy 110-115-128
silver nitrate solution 124
streptomycin 110
thromboplastic 118
thoracoplasty 111-112-114-122-123-124-125
treatment types of 109-110
tuberculosis 122
types 118-121
ulcers 124
vaccines 128
Tuberculous bacillus 129
Tuberculous cysts 130
Tuberculous epidermids 139
Tuberculous meningitis 60-63
blood levels 61
dihydrostreptomycin 111
management of patient 111
para-aminosalicylic acid 111
protein 60
mortality rate 60
spinal fluid levels 61
streptomycin 60-62
toxicity of streptomycin 111
Tuberculous prostatitis 129-130
Tularemia 77-80
automycin 77
bed rest 77
buboes 78-79
cyanosis 78
deafness 80
diarrhea 78
diet 77
enteric infection 78
heat applications 78
lymphadenitis suppurative 78-79
magnesium sulfate 78
oxygen administration 78
penicillin 78
streptomycin 77-78-79
terramycin 202
toxicity of streptomycin 79
vertigo 80
Tweezers 80 in spruce budworm 308
Typhoid fever 88-89-199-203-317
bed rest 90
carriers 92
chologlycine 89-90-92
cholera 92
circulatory collapse 91
complications 90-91-92
convalescent period management of 91
diarrhea 90-91
dysentery 90
glucose 91
hypophysis 317
glucose 91
intestinal hemorrhage 91
intestinal perforation 92
myocarditis 91
osteomyelitis 92
oxygen administration 91
prophylaxis 89
shock 91
streptomycin 91
sulfaguanidide 92

- Typhoid fever—(continued)**
 sulfasuxidine 92
 terramycin, 199 203
 thrombophlebitis 91
 transfusion of whole blood 91
 treatment, 89 92
 vaccination, 89
- Typhoid vaccine**
 intermittent hydroarthrosis 550
 toxoplasmosis, 155
 Typhoid fever, 243 244 299 20*
- Typhlitis**
 arterioocclusion obliterans 464
 bronchiectasis, 371, 373
 bronchitis, chronic 373
 emphysema 375
 thromboangitis obliterans 464
- Ulceromembranous stomatitis 314**
- Ultraviolet light**
 angioneurotic edema 534
 eczema nummular 633
 psoriasis 630
 urticaria, 584
- Undulant fever**
 (See Brucellosis)
- Ulcer, peptic**
 (See Peptic ulcer)
- Ulcer peptic of esophagus 317**
 Unilateral renal tuberculosis 120
 Unna's paste boot in osteitis deformans 556
- Uremia, 515, 522 524**
 acetylsalicylic acid 555 525
 acidosis 525
 amino acids 524
 ammonophylline, 523
 ammonium chloride 524
 artificial kidney 523
 atropine 524
 barbiturates 523
 calcium gluconate 523
 chloral hydrate 523 524
 codeine 523
 convulsive, 523 524
 diet 522
 diethyl, 522
 diuretics 522
 estradiol 524
 fluid intake 522
 gentamicin 522 523
 glucose 522 523
 intestinal lavage
 magnesium sulfate 523
 molar lactate solution 523
 morphine 523 524
 parathion, 523 524
 peritoneal dialysis 523
 plasma 522, 524
 protein intake 522
 salt restriction 522
 salt solution physologic 522 523 524
 serum albumin 523
 sodium amygdal 523
 sodium bicarbonate 522 523 524
 sodium lactate 524
 venesection 523
 vitamins 522
 xanthine drugs 523
- Urethane**
 leukemia, acute granulocytic 492
 leukemia, chronic granulocytic 493
 494-496
 leukemia, chronic lymphocytic, 497
 multiple myeloma 510-511
- Urticaria 73 74**
 Urinary tract infections, 198 199 200
 201 202 239 344
 Uroastone 320
 Urticaria and angioneurotic edema 305
 532 584
 acute 533 534
 angioneurotic edema, 532 534
 antibiotic use 584
 autohemotherapy 534
 benadryl 584
 calcium 584
 chronic 533 534
 diet 583 584
 drugs caused by 533 584
 endocrine products caused by 583
 epinephrine 584
 etiology 582 583
 foods caused by 583 584
 gallstones 583
 histamine 584
 histamine 584
 hydrochloric acid dilute 584
- migraine 533**
 pancreatic extracts 534
 penicillin 534
 physical agents caused by, 583
 pyridoxamine 534
 sodium thiosulfate 534
 spleen extracts 584
 tarantol 584
 ultraviolet light 534
 vitamin A 305
- Vaccines**
 actinomycosis 130 132
 asthma bronchial 381
 blastomycosis 132 133
 bronchiectasis 374
 bronchitis chronic 374
 cholera 97
 coccidioidomycosis progressive 335
 colitis chronic thrombo-ulcerative 335
 common cold 4
 cryptococcosis 141
 diphtheria 80
 emphysema 374
 glanders 108
 influenza 4 5
 intermittent hydroarthrosis 550
 leishmaniasis, 160
 leptospirosis 148
 monilia 139
 multiple sclerosis 648
 mumps 35
 pertussis 84 85 86
 plague 99
 pneumonia 41
 rabies 19 20 21-22
 rickettsial diseases 143, 144
 Rocky Mountain spotted fever 144
 smallpox, 17, 18
 sporotrichosis, 143
 stomatitis herpetic 315
 tetanus 104
 thromboangitis obliterans 462
 thrombo-ulcerative colitis chronic 338
 typhoid fever 80
 typhus fever 143 144
 yellow fever 35
- Vaccinia**
 (See Smallpox vaccination)
- Vagotomy, 330 341**
 valvular disease chronic 432-432 434
 valvulotomy in cardiac decompensation, 445
 Vagocaine apparatus for arterial therapy 370
- Variella**
 (See Chickenpox)
- Varices esophageal 314, 317**
- Variola**
 (See Smallpox)
- Vascular disease in diabetes mellitus 236**
- Venesection**
 cardiac decompensation 444
 cerebral circulatory disturbances 632
 cerebral hemorrhage prevention of 628
 polycythemia vera 502 503
 uremia gravior 523
- Venous ligation in pulmonary embolism 379 380**
- Ventricular**
 aneurysm pericardial 478
 pericardial infarct, 293
- Vertigo**
 Meniere's syndrome 669 670 671
 tinnitus 80
- Vesiculopustular monilia, 137**
 Vibriosis, 97, 95
 Vincent's angina, 324
 Vincent's organisms in granuloma in gingivitis 162
- Vicodin**
 angina 191
 eczema, nummular 633
 impetigo contagiosa 672
 psoriasis 679
 scabrous dermatitis 679
- Vitamin A**
 absorption 290
 carotene 290 291
 cod liver oil 291
 colitis, chronic thrombo-ulcerative 337
 deficiency 290 291
 diet therapy 290-291
 eczema humillaris 633
 enteritis, regional 333
 glomerulonephritis acute, 314
 hepatitis, toxic, 350
 hypertensive vascular disease 452 454
- hypervitaminosis A 291**
 keratomalacia 290
 keratoris follicularis, 291
 oral administration 291
 osteomalacia, 561
 parenteral administration 291
 polyneuritis rubra 291
 preparations 291 292
 regional enteritis 333
 requirements 290
 sprue syndrome 307
 stomatitis gangrenosa, 315
 storage, 290
 thrombo-ulcerative colitis chronic 337
 toxicity, 291
 xerophthalmia 290
- Vitamin B complex**
 acne 674
 alcoholism acute 601
 anemia pernicious 473
 bacillary dysentery 95
 barbiturate poisoning 608
 cell acid syndrome, 366 367
 carcinoma of the liver portal 333
 colitis chronic thrombo-ulcerative 338
 enteritis regional 333
 epilepsy, 658
 glomerulonephritis, acute 314
 hepatic insufficiency 356
 hepatitis toxic 350
 monilia 139
 lichen planus 681
 liver acute yellow atrophy of, 331
 methyl alcohol poisoning 603
 neuritis 667
 pancreatitis acute, 364
 pancreatitis chronic 361
 preoperative preparation of jaundiced patient 359
 obesity 243
 rabies 21
 regional enteritis 333
 scabrous dermatitis 679
 stomatitis gangrenosa 313
 thrombo-ulcerative colitis chronic 338
 vitamin B₁₂ (thiamine chloride) absorption 292
 beriberi 292 293
 colitis chronic thrombo-ulcerative 337
 deficiency 292 294
 diabetes mellitus 293
 glomerulonephritis acute 314
 gout caused by, 348
 hypertensive vascular disease 452
 neurasthenia, 291
 neuritis 100, 667
 polioencephalitis acute 293
 preparations 293 294
 psoriasis 679
 pulmonary abscess 583
 requirements 292
 storage 292
 thrombo-ulcerative colitis chronic, 337
 toxicity 293
 Wernicke's disease 293
- Vitamin B₁₂ (thiamine)**
 absorption 296
 chelation, 296
 deficiency 296 297
 diet therapy 296
 hypertensive vascular disease, 452
 monilia 139
 oral administration 296 297
 parenteral administration 296 297
 preparations 297
 requirements 296
 storage 296
 toxicity 297
- Vitamin B₆ (pyridoxine)**
 leukemia chronic granulocytic 494
 neuritis 667
- Vitamin B₁₂**
 anemia, macrocytic of nutritional deficiency 481
 anemia macrocytic of infancy 481
 anemia pernicious 478 479 480
 celiac syndrome 367
 sprue syndrome 307
- Vitamin C (ascorbic acid)**
 absorption 297
 anemia 295 299
 arteriosclerosis 465
 arterioocclusion obliterans 465
 bacillary dysentery 95
 beriberi 293
 cell acid syndrome 366 367
 colitis chronic thrombo-ulcerative 338
 deficiency 297 299
 detoxification 299

- diet therapy in scurvy 297 298
 dissecting aneurysm of the aorta, 456
 diphtheria 83
 gastro-intestinal complications of per-
 tussis 88
 enteritis regional 333
 gingivitis 299
 glomerulonephritis acute 314
 chronic 321
 hepatitis toxic 350
 mercublydren 299
 pancreatitis acute 364
 pancreatitis chronic 365
 preoperative preparation of jaundiced
 patient 359
 preparations 299
 pulmonary abscess 384
 regional enteritis 333
 requirements 297
 rheumatic fever 70
 scurvy 297 298
 Sippy diet 298
 smallpox 17
 sprue syndrome 308
 stomatitis gangrenous 315
 storage 297
 thromboangitis obliterans 465
 thrombo-ulcerative colitis chronic 338
 toxic ty 299
 Vincent's angina 314
 wound healing 299
- Vitamin D**
 arthritis 302
 absorption 299
 calcium 299 301
 calcium gluconate 301
 calcium lactate 301
 cat liver oil 302 302
 deficiency 299 302
 drusol 299 302
 eczema nummular 683
 foods fortified 302
 glomerulonephritis acute 314
 hypertensive vascular disease 451
 hypocalcemic triad 301 302
 hypoparathyroidism 273 274 275
 infants normal 300
 premature 300
 laryngospasm 301
 nephritis 301
 oral administration 300
 osteomalacia 301 360 361
 osteoporosis senile 301
 parenteral administration 300
 peromorph oil 300 302
 phosphorus 299
 poliomyelitis acute 27
 preoperative preparation of jaundiced
 patient 359
 preparations 302
 requirements
 adults 300
 children 299-300
 rickets 300 301
 single dose therapy 300
 sources in foods 300
- apraxia syndrome 308
 stomatitis gangrenous 315
 storage 299
 sunlight 299 300
 tetany hypocalcemic 301-302
 toxicity 302
 viosterol 299 300 302
 Vitamin deficiencies 288 307
Vitamin E
 angina pectoris 412
 arteriosclerosis obliterans 465
 coronary insufficiency 412
 osteomalacia 361
 scleroderma 472
 sterility male 284
 thromboangitis obliterans 465
Vitamin K
 absorption 303 304
 arterial occlusion sudden 468
 cholecystitis acute 360
 colitis chronic thrombo-ulcerative
 338
 deficiency 303-306 307
 dicumarol 305
 dissecting aneurysm of the aorta 456
 enteritis regional 333
 erythroblastosis fetalis 488
Escherichia coli 303
 gastro-intestinal disorders 304
 hemorrhage 303 304 305
 hepatic insufficiency 355 356
 hepatitis 38 350
 hyaline 306
 hypoproteinemia 303 304 305
 381
 intestinal hemorrhage 91
 leptospirosis 148
 liver acute yellow atrophy 352 352
 menadione 304 305 306
 menorrhagia 305
 myocardial infarction bleeding in 420
 osteomalacia 361
 pancreatitis acute 364
 phlebotomiasis 476
 parenteral administration 303 304
 preoperative preparation of jaundiced
 patient 359 359
 preparations 305 306
 prothrombin 303 304 305
 prothrombinopenia 305
 regional enteritis 333
 requirements 303
 sources in foods 303
 steatorrhea 304
 sprue syndrome 308
 storage 303
 sudden arterial occlusion 468
 synkamin 306
 synkamin 306
 toxicity 305
 thrombophlebitis 476
 thrombo-ulcerative colitis chronic 335
 tuberculosis 128
 uric acid 305
Vitamin P 350
 Vitamin requirements 288 289
- von Bechterew's disease
 (See Arthritis rheumatoid)
 Vulvovaginitis 138
- Wangensteen suction for gastric dilatation
 364
 Waterhouse-Friderichsen syndrome 49
 Water trap in spontaneous pneumothorax
 388
 Weber-Christian disease 197
 Weil's disease 347 349
 Wernicke's disease 293
 Western cutaneous leishmaniasis 180
 Whitfield's ointment 673 684
 Whitmore 109
 Whooping cough
 (See Pertussis)
 Wilder diet 407
 Wilson's disease 651
 Wood alcohol poison ing
 (See Methyl alcohol poisoning)
Wuchereria bancrofti 214
Wuchereria malaya 214
- Xanthines**
 angina pectoris 411-412
 cardiac decompensation 440
 cerebral arteriosclerosis 633-634
 coronary insufficiency 411-412
 glomerulonephritis chronic 321
 headache 639
 myocardial infarction acute 418
 uremia genuine 322
Xanthomas in diabetes mellitus 240
 Xerophthalmia 290
- Latent in amebiasis 191
- Yaws**
 (See Tropical treponematosis)
 Yellow atrophy of the liver acute
 (See Acute yellow atrophy of the
 liver)
 Yellow fever 34-35
- Zephiran chloride solution aqueous 17
 Zinc ascorbate 137
Zinc oxide
 eczema atopic 682
 eczematous contact dermatitis 683
 dermatitis herpetiformis 678
 erythema multiforme 677
 lichen planus 681
 monilia 137
 pityriasis rosea 680
 pruritus ani 684 685
 psoriasis 679 680
 seborrheic dermatitis 679
 tinea cruris 674
 tinea glabra 674
 tinea manus 676
 Zinc salt poisoning 321
 Zinc stearate 10
 Zirconium

